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Vol. 23 JANUARY, 1948 No. 1

SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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Published by THE C. V. MOSBY COMPANY, St. Louis, U. S. A.

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Vol. 23, No. 1, January, 1948. Surgery is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription price: United States, its possessions, Pan-American Countries, $10.00 a year; Canada and Foreign, $11.00. Entered as Second-Class Matter January 20, 1937, at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Printed in U. S. A.

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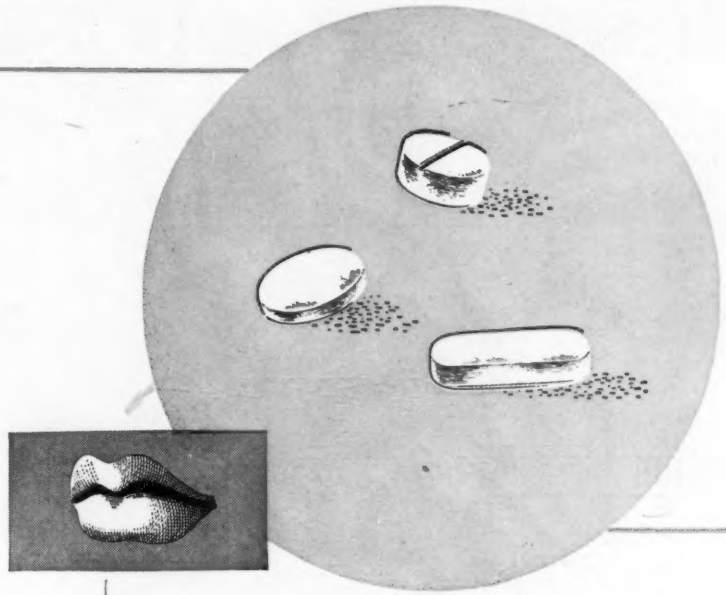

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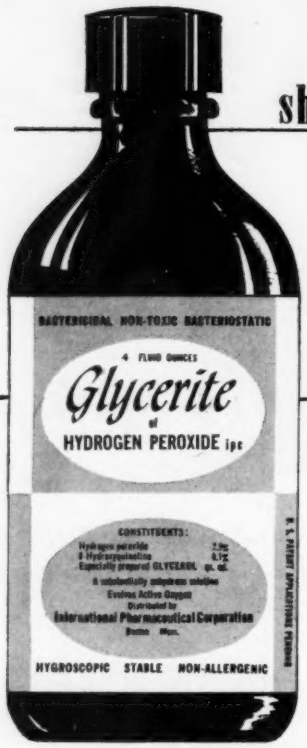

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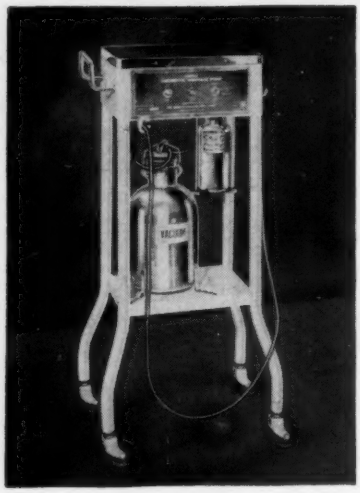

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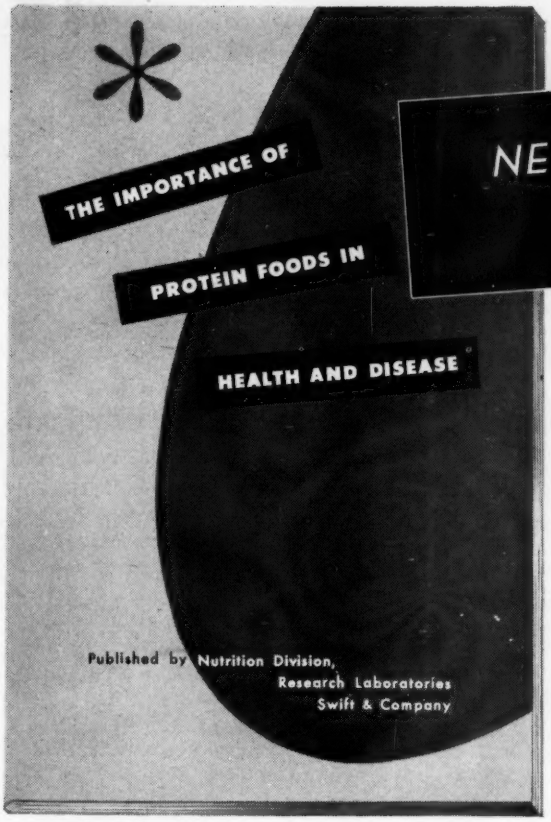

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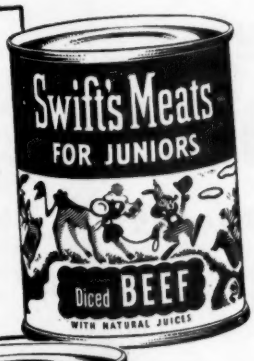

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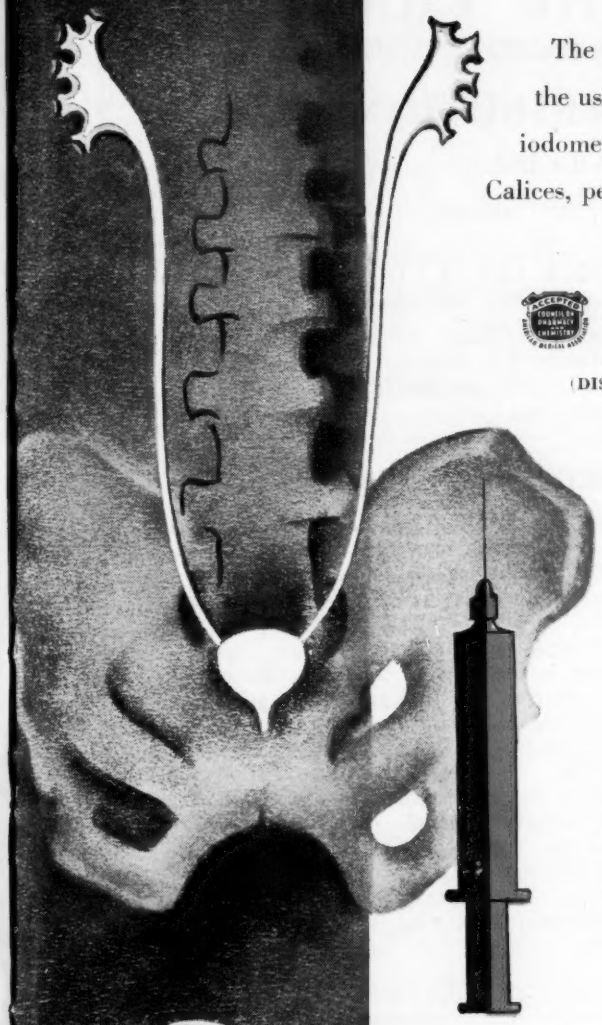

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VOL. 23 JANUARY, 1948 NO. 1

Original Communications

THE ARTERIAL BLOOD SUPPLY OF THE COMMON AND HEPATIC BILE DUCTS WITH REFERENCE TO THE PROBLEMS OF COMMON DUCT INJURY AND REPAIR

BASED ON A SERIES OF TWENTY-THREE DISSECTIONS

ALFRED L. SHAPIRO, M.D., AND GREGORY L. ROBILLARD, M.D., BROOKLYN, N. Y.

(From the Surgical and Pathological Services of the Brooklyn Cancer Institute, Beth El, and Norwegian Hospitals)

IN THE course of a study, appearing elsewhere, on the morphology and variations of the duodenal blood vasculature in relation to the problem of post-gastrectomy duodenal stump leakage, we[80] had frequent occasion to trace the small blood vessels supplying the ductus choledochus. In attempting to compare our findings with previous anatomic descriptions, review of some thirty treatises, atlases, dissection manuals, and applied texts[1-30] failed to disclose any definitive consideration of the blood supply of the biliary passages proper, although considerable detail on the variational anatomy of the hepatic arteries was generally incorporated. Painstaking search of the literature revealed no reasonably complete study of the topic; however, a few writers[32, 34, 40, 48, 49, 66, 76] briefly referred to one or more small arteries actually or presumably supplying the bile ducts. Contrary to our observations, these vessels were generally indicated as arising primarily from the hepatic arteries.[16, 32, 34, 42, 48] A single fairly recent foreign paper, comprehensive and well executed, dealing with the venous circulation of the extrahepatic ductal system, but without reference to its arteries, was encountered.[54] No articles in the English language journals were found, and with few exceptions the meager depications appear to be relatively at variance with our findings.

The greatly increased clinical importance of bile duct surgery in recent decades warrants, in our opinion, this somewhat detailed re-presentation of its blood supply. The voluminous literature and discussions of common duct injury incident to surgery and the numerous operative descriptions of reparative, reconstructive, or the newer radically resective procedures apparently omit all consideration of the intrinsic blood supply of this tube.[38, 41, 67-71, 74, 75, 77, 88]

Received for publication, April 29, 1946.

Accurate knowledge of the origins and distribution of these delicate vasa propria may be of great significance if the bile ducts are correctly considered as analogous to gut from the surgical point of view.[79] It is well established that the viability of enteric segments involved in various surgical technical procedures is primarily dependent on maintenance of an adequate circulation. Carter and Maraffins,[67] Allen[70] and Cole,[71] among others, stress the advisability of securing mucosal lined rather than fistulous channels in hepatic or common duct plastic procedures without, however, emphasizing the need to safeguard the blood supply of structures utilized.

The hepatic and common ducts in rudimentary fashion resemble small intestine in structure.[85-88] The mucosal lining, tunica muscularis, and serosa or tunica propria of the 7.0 cm. to 8.5 cm. long ductus would appear to require an adequate circulation for viability no less than similar endodermally derived tissue elsewhere. The possible role that devascularization and consequent ischemic necrosis (secondary to stripping a large cuff or surface of these ducts), might play in the formation of strictures and fistulas, or in the failure of duct reconstructions and choledochoenteroanastomoses, does not appear to have been given suitable consideration. As cited in greater detail in our papers on duodenal and colonic arterial supply, Welsh and Mall, as quoted by Eisberg,[46] Rothschild[57] and other investigators reported that mesenteric ligations of the intestinal vasa recta effectively devascularizing segments as little as 3 to 5 cm. in length produce gangrene of the loop. The intestinal vasa recta are considerably larger and relatively more abundant than the vessels demonstrably supplying the biliary ducts. Anastomotic marginal arteries running the entire length of the common duct and insuring sufficient circulation with relatively complete stripping appear to be infrequent. More often than not small blood vessels approaching almost at right angles to the ducts appear to serve as end arteries for segments several centimeters long and are so arranged that widespread separation of the structures in the hepatoduodenal ligament might lacerate these relatively fine trunks. To what extent such manipulation might result in localized ischemic necrosis and later unexpected stricture formation, so-called spontaneous postoperative rupture, fistulas, or failure of anastomatic procedures, is a problem for the solution of which experimental surgery is indicated. At present we are investigating the effect of such devascularization in animal surgery, utilizing fluorescein and ultraviolet light as an adjuvant method, as advocated by Lange[97] and others, to determine circulatory adequacy. On completion of these studies a detailed report is contemplated. However, it is our present impression that minimal stripping for surface exposures, particularly along the medial border, is probably advisable under most circumstances in order to reduce the danger of devascularization and ischemic necrosis in common duct surgery. As a rule, the cystic and hepatic arteries can be suitably identified without denuding too great a segment of bile duct. It should be noted that in dilatation of the common duct its tiny blood vessels often hypertrophy to a size readily discernible in nonfatty hepatic pedicles.

ARTERIAL DISTRIBUTION TO THE BILE DUCTS

The following survey of the arterial circulation of the extrahepatic biliary passages is drawn in the main from our own investigations and to some extent from the several sources quoted. Dissections were made of twenty-three bodies, all refrigerated, of individuals who had died less than two days before. The anatomic studies were made in the course of complete necropsy and no cases were included where pathology or extreme obesity existed of such a nature as to obscure the structure of the celiac and superior mesenteric trunks or branches. India ink injected[44] in the ligated hepatic, gastroduodenal, and superior mesenteric arteries was utilized for contrast filling of small arteries. For demonstration of the detailed distribution of the ductal vasa propria they were often cannulated by blunted hypodermic needles of small size and injected with India ink from a 1 c.c. tuberculin syringe. Unless otherwise specified, figures given are derived from this series of cases. Corroborative or explanatory reference citations are often indicated by number alone. In studies of this nature no claim for originality of observations can very well be made. Our intent is rather to collate and amplify the meager, widely scattered, and hitherto somewhat inaccessible information available on this somewhat neglected topic. In all probability prior descriptions exist but are difficult to trace.

In our material the small branches supplying the common and hepatic ducts showed great variation in distribution. It would appear possible, as pointed out by us with reference to the arterial supply of the duodenum[80] and transverse colon,[81] that in certain cases a scanty configuration of supplying twigs may render the individuals concerned especially prone to operative ischemic injuries to the bile ducts with resultant fibrosis or fistula formation. Certainly the subject with only two or three demonstrable vessels runs a greater risk of devascularization with one or two small trunks injured than does a person with biliary passages completely ringed by the elaborately ramifying branches of a half-dozen or more proximate arteries. In a fairly thoroughly review of the literature on the possible causes of bile duct injury, a brief statement by Dragstedt and associates[72] that the blood supply of the biliary passages themselves might be involved was the only consideration given to this obvious etiologic factor.

The usual explanations[67, 69, 70, 71, 77, 89-96] given for so-called benign strictures of the common bile duct concur in attributing them, in by far the majority of instances, to cholecystectomy. Occasionally a local stricture at the junction of cystic and choledochal ducts is found, possibly secondary to inflammation, abscess, or choledochostomy. Most writers[67, 70, 89, 91-93, 96] stress the etiologic rule of inadvertent clamping, ligation, section, or excision of a segment of non-visualized duct. Cattell[96] and Lahey[92] pointed out the danger of injury to the intrapancreatic termination of the duct in duodenal mobilization secondary to subtotal gastrectomy. Calculus ulceration, chronic sclerosing pancreatitis,[94] necrotization by activated pancreatic reflux into the biliary passages,[89] and obliterative cholangitis[93] have been proposed as nontraumatic causative factors.

However, known cholangitis and cholelithiasis are conditions often escaping surgery without the recorded development of stricture formation, whereas the obliteration of the ducts in several hundred reported cases in the literature has almost invariably followed surgery. The premise that factors other than traumatic are frequently responsible would, therefore, in our opinion, be unsubstantiated.

Inasmuch as benign postsurgical fibrotic obliteration of the common bile duct is, in the majority of cases, observed to be extensive or even complete, the possibility of devascularizing injury (followed by similar fibrotic degeneration in ischemic gut) deserves consideration. Since often only the uppermost hepatic or the lowermost intrapancreatic segments are spared, that part of the duct supplied as a rule by twigs from the cystic arteries or less usually by the right hepatic artery appears to be most commonly involved.

The retroduodenal portion of the common duct usually receives three to five twigs from the superior posterior pancreatic duodenal artery as it loops around the common duct.[40, 53, 66] The existence of a posterior pancreaticoduodenal arcade as a constant structure, as discussed in our paper on the duodenal vasculature, is mentioned in only three[2a, 5, 88] of some thirty standard anatomy treatises, texts, and atlases. Pierson,[53] Petren,[55] Ramodnowskaja,[58] Wilmer,[62] and Ziegler,[64] among other recent writers,[31, 43, 45, 50, 63] confirm the presence of both an anterior and a posterior pancreaticoduodenal arcade in from 75 to 80 per cent of human bodies. Quoting our own previously published findings,[80] "the posterior superior pancreaticoduodenal artery generally originates independently from the right dorsal side of the gastroduodenal and in 75 per cent of cases as it descends crossed anteriorly to the right of the retroduodenal common bile duct, curves round it, and, crossing it dorsal to its intrapancreatic portion, descends toward the left thus usually forming an arterial hook around the duct, contributing to it several small branches at the same time. One or more of these twigs extends along the common duct and may form an accessory cystic."

Since it is noted[37, 40, 53] that the most important twigs to the lower ductus choledochus as a rule stem from a sizable vessel, the posterosuperior pancreaticoduodenal artery, which itself has received insufficient anatomic or surgical recognition, it is small wonder that the intrinsic blood supply of the duct proper has been accorded even less attention as a primary subject.

In two of our cases the supraduodenal artery,[61, 62] in both instances larger than usual, gave a discernible branch to about the junction of the lower and middle thirds of the common duct. Here the unusually prominent supraduodenal artery notably overlapped the region of duodenum usually supplied by the superior pancreaticoduodenals. The right hepatic artery, as described many years ago by Haller,[34] may contribute several small branches to the central and upper secetions of the ductus choledochus. We have found such branches with relative constancy, but disagree with Rouviere,[16] Soulsloff,[36] and Faure[48] as to their importance. In accordance with Branco[40] our impression is that these hepatic artery twigs are generally so fine and minute as to

contribute only a minor part of the choledochal blood supply in most instances. However, in two of our cases, with a low or common trunk origin of the posterosuperior pancreaticoduodenal the apparently replacing branches came primarily from the right hepatic artery. In another two cases the posterosuperior pancreaticoduodenal arose from the hepatic, and in both of these instances the gastroduodenal and common hepatic arteries gave definite twigs to the common bile duct, which in one example ascended as an accessory cystic, a finding noted also by Branco[40] and Michels[66] and apparently illustrated by Belou[28] in a single figure. Flint,[49] Haller,[34] and Descomps[37] in picturing a fair-sized branch of the gastroduodenal or hepatic artery passing directly to the lower anterior surface of the common bile duct appear to have described the exceptional rather than the regular modes of supply. Descomps,[37] however, noted that the precholedochal ascendant branch might arise from the pancreaticoduodenal arcades.

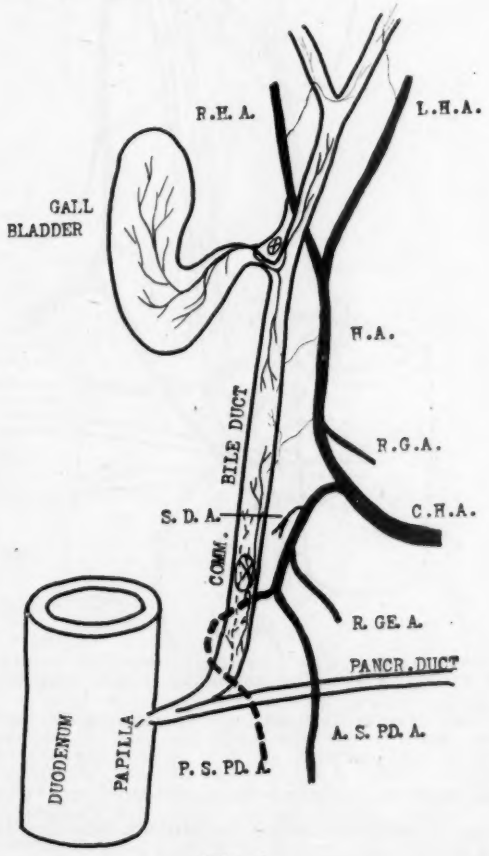

Fig. 1.

Fig. 2.

Fig. 1.—Usual supply. Note looping of posterosuperior pancreaticoduodenal artery around retroduodenal portion of common duct and origin of ascending and postcholedochal twigs from loop. The right hepatic artery may pass anterior or posterior to the duct. Cystic arterial branch to the duct is of fair size; rami from hepatic arteries are minute and fine. *R.H.A.*, right hepatic artery; *L.H.A.*, left hepatic artery; *C.H.A.*, common hepatic artery; *R.G.A.*, right gastric artery; *S.D.A.*, supraduodenal artery; *A.S.PD.A.*, anterospuperior pancreaticoduodenal artery; *P.S.PD.A.*, posterosuperior pancreaticoduodenal arteries; *R.GE.A.*, right gastroepiploic artery; *H.A.*, hepatic artery.

Fig. 2.—Double cystic artery supplying increased number of descending twigs (four cases). Devascularization would ensue if twigs were lacerated at sites marked by crossed ellipses.

The cystic arteries likewise, as stated also by Faure,[48] send small arterial channels to the upper part of the common duct and, where the bifurcation is low, to the right hepatic duct. Both right and left hepatic arteries may send fine almost hairlike vessels to the extrahepatic segment of the hepatic ducts. Occasionally (two cases) when the ascending branches along the retroperitoneal and posterior segment of the choledochal tube are not strongly developed, the

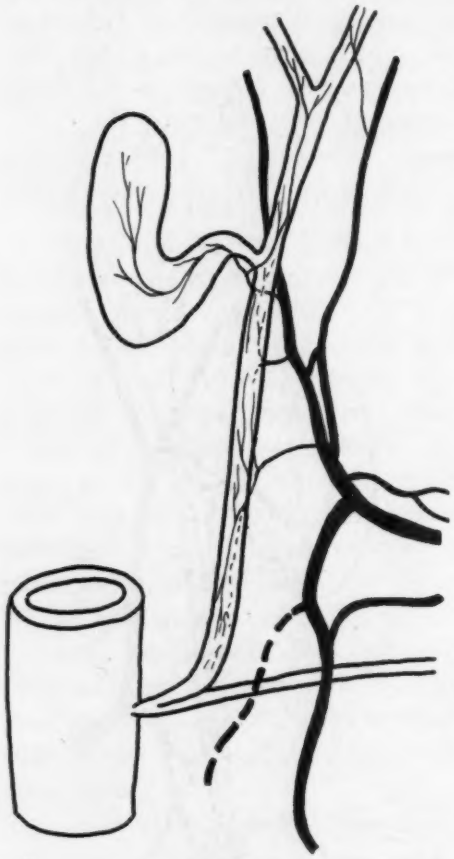

Fig. 3.

Fig. 4.

Fig. 3.—Replacing arteries from right hepatic; low origin (common trunk) of antero- and posterosuperior pancreaticoduodenal vessels without looping or ascending ductal branches (two cases).

Fig. 4.—Composite supply; several fairly well developed twigs from cystic, hepatic, and posterosuperior pancreaticoduodenal arteries (one case).

cystic or right hepatic artery may provide a usually well-defined descending twig or two which may be traced anteromedially particularly, to almost the lower third of the common duct. Calot, as cited by Branco,[40] appears to have considered this, contrary to our experience, as a typical finding.

Several diagrammatic sketches of the arterial branches to the common bile duct that we have encountered are illustrated in Figs. 1 to 6 to depict the more usual sources of supply as well as the hooking of the posterosuperior pancreaticoduodenal artery around the retroduodenal portion of the common bile duct. At the points indicated by the crossed ellipses, laceration during operation of

the arterial branches to the duct proper, or vasa propria, which seem to be functional end-arteries, would apparently devascularize a segment several centimeters long. The dotted lines indicating twigs along the posterior aspect of the common bile duct and hepatic ducts should be borne in mind. As has occurred with the concept of the pancreaticoduodenal circulation, surgeons and anatomists are prone to visualize only the anterior blood supply of these organs. However, as in the case of the small intestine,[44, 46, 47, 56] it is likely that neither

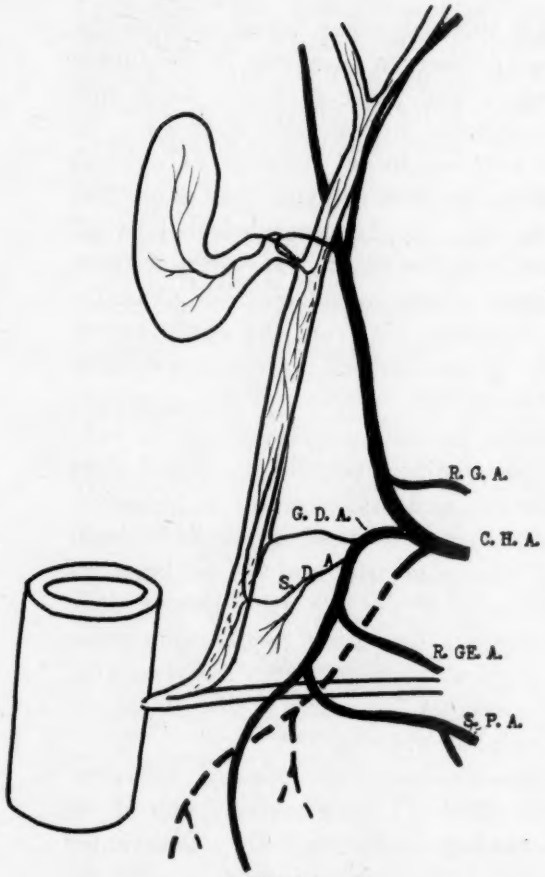

Fig. 5.

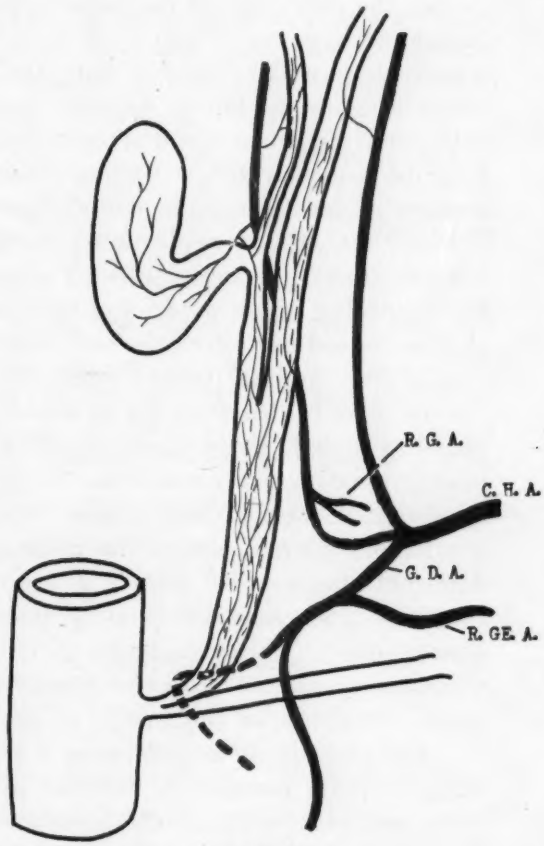

Fig. 6.

Fig. 5.—Origin of superoposterior pancreaticoduodenal artery from common hepatic, superior pancreatic from gastroduodenal; replacing ascending choledochal arteries from gastroduodenal and supraduodenal vessels (one case). *R.G.A.*, right gastric artery; *G.D.A.*, gastroduodenal artery; *C.H.A.*, common hepatic artery; *S.D.A.*, supraduodenal artery; *R.GE.A.*, right gastroepiploic artery; *S.P.A.*, superior pancreatic artery.

Fig. 6.—Ringing of ducts by multiple ascending and descending twigs with elaborate pericholedochal anastomosing arterial plexus. Incidental low bifurcation of hepatic ducts and arteries illustrated (three cases). *R.G.A.*, right gastric artery; *C.H.A.*, common hepatic artery; *G.D.A.*, gastroduodenal artery; *R.GE.A.*, right gastroepiploic artery.

anterior nor posterior twigs provide a completely circumferential anastomosis and that both sets of vessels are necessary to secure adequate blood supply. Histologic studies to determine this point are in progress.

An accessory cystic artery, reported by Flint[49] and other authors[51, 59] as present in about one-sixth of bodies dissected, occurred in three cases, arising in two from the hepatic and one from the gastroduodenal. Only in the latter in-

stance did it provide rami of any size to the bile duct. In none of the cases studied in detail for this report was any remarkable anomaly of the hepatic arteries encountered, therefore we are unable to describe what variations occur in the choledochal blood supply in these cases.[41, 52, 73] Similarly, no accessory or anomalous hepatic or cyst ducts were noted. A retroductal position or low bifurcation of the hepatic vessels, or low division of the common duct, either occurring in about one-quarter and likely to coexist, is not considered abnormal for purposes of this paper.

In the dissection of the hepatic pedicle tiny arteriolar branches from the hepatic arteries, noted also by Branco,[40] were observed to course to the larger lymph nodes and ganglia of both the pedicle and porta hepatis. As a rule the arteries to the biliary passages ran lengthwise for variable distances. In only three instances could a noteworthy pericholedochal network of arterial loops be demonstrated, a finding referred to by Wiart,[32] and Guillaume[35] as a cause of hemorrhage in denuding or incising the hepatocholedochal canal. Friend[76] stated that a plexus of veins and arteries covers the common duct, but reference to his accompanying illustration reveals nonanastomosing ramifying branching of an anterior descending arterial twig from the cystic artery and an ascending anterior vessel from the gastroduodenal in the occasionally encountered prolific pattern referred to previously.

In three bodies, from six to nine branches, ascending and descending, were found to encircle the common duct, the upper coming from the cystic and right hepatic arteries, the lower from the gastroduodenal and superior pancreaticoduodenal. Some of these vessels, however, seemed to form a pericholedochal anastomotic plexus between the cystic and hepatic arteries and the pancreaticoduodenal vessels which did not afford tributaries to the bile ducts proper since they could be easily lifted away intact without lacerating any demonstrable vasa propria. This was, however, not a typical arrangement. No vessels of significance appeared to enter the biliary passages from any of the retroperitoneal structures or the gastric or gastroepiploic arteries.

For purposes of completeness a brief description of the veins of the extrahepatic biliary passages is included in this paper. In our material the upper veins ascended to the porta hepatis. According to Petren[54] they then enter the hepatic vein radicles directly. As a rule, the lower veins drain only the lowermost portion of the common duct and empty into the portal vein. Rouviere,[16] Faure,[48] and Branco[40] portrayed a venous anastomosis between hepatic and portal systems along the common bile duct and indicated that the major venous drainage of the bile ducts is downward and into the portal vein via the superior pancreaticoduodenal or gastroduodenal veins. In several bodies, however, we found that injection of the portal vein filled only the lowermost venules primarily of the retroduodenal portion of the common duct, an apparent substantiation of Petren's[54] contention that the venous drainage of both gall bladder and biliary ducts is into the hepatic vein radicles directly, without major anastomoses between the portal and hepatic venous systems. For this reason, he claimed,[54] there is no dilation of veins along the common bile duct in hepatic cirrhosis.

SUMMARY

The proximate and intrinsic circulation of the ductus choledochus and the hepatic ducts is described as present in twenty-three bodies dissected. The possible etiologic significance of ischemic necrosis in common bile duct and hepatic injury, as obliterative fibrosis, rupture, or fistula formation, or failure of reconstructive ductal anastomoses is considered. The important arterial branches to the common and hepatic ducts are demonstrated as arising primarily from the cystic and posterosuperior pancreaticoduodenal arteries rather than the hepatic artery, as usually represented in the few prior descriptions available in the literature. The venous drainage of the extrahepatic biliary passages ascends in the main to empty directly into the hepatic vein radicles without demonstrable major anastomoses with the portal system.

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UNUSUAL INNERVATION OF THE INTRINSIC MUSCLES OF THE HAND BY MEDIAN AND ULNAR NERVE

EUGENE E. CLIFFTON, M.D., NEW HAVEN, CONN.

IN THE course of examining a large number of peripheral nerve injuries, in a neurosurgical and hand surgery center, it was surprising to find cases in which the innervation of the small hand muscles, apparently, was through unusual channels. Reports of several of these cases were first presented at the Hand Conference at Wakeman General Hospital late in 1945.

The usual innervation of the small hand muscles as described in standard anatomic and peripheral nerve texts is as follows:

MEDIAN	ULNAR
Flexor pollicis brevis	Adductor pollicis
Opponens pollicis	Lumbricales, 3 and 4
Abductor pollicis brevis	Dorsal and palmar interossei
Lumbricales, 1 and 2	Abductor digiti quinti
	Opponens digiti quinti
	Palmaris brevis
	Flexor digiti quinti brevis

It is considered common for the flexor pollicis brevis to have dual innervation, the medial head by the ulnar and the lateral head by the median.

In the cases to be reported, partial function of these muscles remained despite complete section of the nerve involved, either median or ulnar. This same observation has undoubtedly been made by others and five cases with partial function were reported by Murphy and associates.[1] It has not been common knowledge, however, even among neurosurgeons and hand surgeons. Brief mention of the condition has been made in the excellent books on peripheral nerves by Pollack and Davis[2] and Haymaker and Woodhall,[3] and in the report of the Medical Department in World War I.[4] A very complete discussion of the entire problem may be found in the text by Stookey.[5]

In discussing any of these unusual innervations it is well recognized that certain false, trick, or anomalous movements may lead one astray unless great care is taken in the muscle test. It is also well recognized that the only absolute proof of muscle function is palpation of the muscle in its actual contraction, or else palpation of motion of the tendon. However, where this is impossible, one can with a fair degree of accuracy rule out false motions, if strict adherence to the type of motion is insisted upon. Furthermore, one can practically rule out false motion by observations of other muscles and tendons which must take over the function of the muscles being tested. For instance, in testing for the interosseus by motion, the contraction of the extensors of the fingers can be easily visualized and palpated if they are taking over the indicated function.

Received for publication, April 12, 1947.

Although false motion cannot be completely and absolutely ruled out, it was felt that the careful check system used in these cases made the findings fairly definite. Other observations are also important in confirming an opinion that incomplete paralysis is present where a complete paralysis is expected. These include lack of the usual atrophy and, in the case of an ulnar nerve lesion, the absence of an ulnar Griffe. In all the cases to be reported atrophy was absent or minimal and ulnar Griffe was absent or minimal. All nerve checks were made in the nerve laboratory, the staff of which consisted of at least one specially trained medical officer and one specially trained physiotherapist whose sole work was a disinterested testing of each peripheral nerve case by voluntary and electrical tests. Each case was then rechecked by at least one other member of the neurosurgical staff. These tests were performed at least one time preoperatively, one month postoperatively, and at three-month intervals until the patient was discharged. Standard methods of examination were used, especially as outlined in the standard texts on peripheral nerves (Pollack and Davis,[2] Haymaker & Woodhall[3]).

The cases to be described were drawn from a total group of over 3,000 cases of nerve injuries, all of which were carefully observed and followed as outlined. Of this total group we have accurate and complete records on 250 ulnar nerve, 150 median nerve, and 151 combined median and ulnar nerve injuries. Of this group neurorrhaphies were performed on 143 ulnar nerves, 81 median nerves, and on both nerves in 36 cases.

All photographs were produced in the routine manner to show function of the involved muscles, with the usual precautions to prevent false motions. The charts are reproduced exactly as they were found in our files.

The voluntary tests are marked on the approximate basis of 0, no function; 1, just perceptible contraction, 2, 25 to 50 per cent of normal; 3, 50 to 75 per cent of normal; and 4, normal.

In the electrical tests F indicates response to faradic current, but with an asterisk it indicates only sluggish response. G_3 indicates a brisk response to galvanic current. Only a faradic response is considered evidence of normal innervation by this test.

CASE REPORTS

Attention was first drawn to this interesting condition on Dec. 29, 1944, shortly after the admission of the first patient (Case 1).

CASE 1.—This soldier received a severe penetrating wound of the posteromedial forearm 8 cm. below the condyles of the humerus, Sept. 24, 1944. Thirty-one hours later at the Fifteenth Evacuation Hospital a débridement with removal of the shell fragment from the anteromedial forearm and suture of the ulnar nerve with closure of the wound was performed. It is of particular interest that the approximation was by a single sling suture of silk and that the nerve ends were still separated by 1 cm. at closure, despite great tension. On the first examination at the nerve laboratory, Wakeman General Hospital, he was found to have voluntary function of all but the palmar interosseous 3, and faradic response on all ulnar nerve muscles, but with anesthesia in the ulnar distribution. Atrophy was minimal. At operation, Feb. 8, 1945, a branch of the medial antibrachial cutaneous nerve was found divided but unsutured and the ulnar nerve was found to contain a neuroma with the silk

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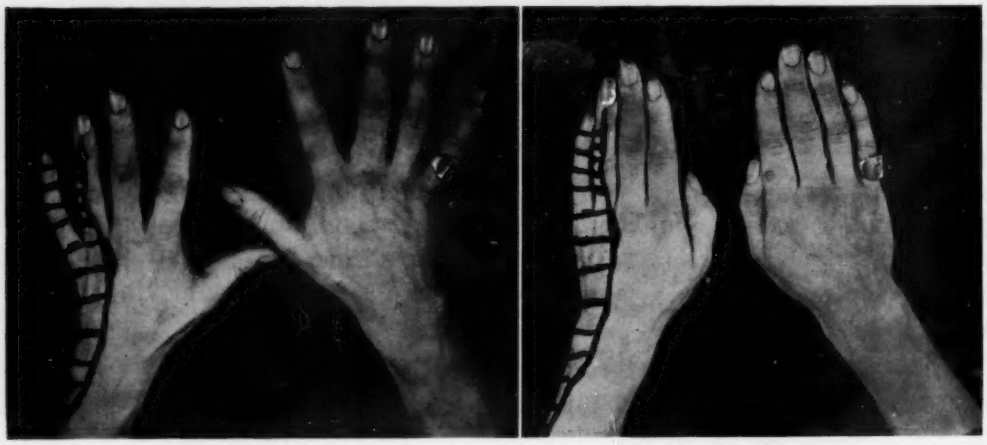
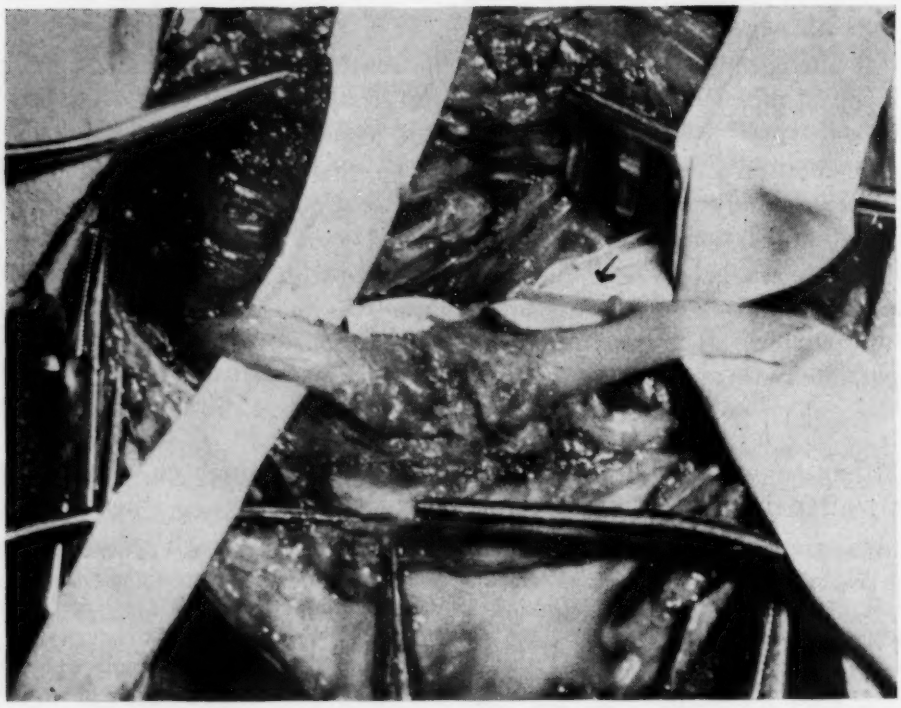
suture imbedded in its center. Stimulation of the nerve above the neuroma resulted in very slight contraction of the small hand muscles. As the dissection was extended, however, a nerve fiber was found to enter the ulnar nerve below the neuroma. This fiber extended upward and medially and was found to originate from the median nerve. A small fiber left the ulnar nerve just above the neuroma and joined this cross fiber (Fig. 1, *C*). Stimulation of the cross fiber resulted in contraction of all the ulnar small hand muscles. A secondary



A. *B.*



C.

Fig. 1.—*A* and *B*, Note ability to spread and approximate fingers and lack of atrophy. Anesthesia area is outlined. *C*, Operative photograph showing scarring and neuroma formation. The arrow points to the communicating branch from the median nerve entering the ulnar below the neuroma. The branch leaving the ulnar nerve to join this communicating branch can just be seen as it passes over the cottonoid at the neuroma level.

partial neurorrhaphy was performed leaving the cross fiber intact. The nerve chart of this patient (Table I) shows his further course graphically (Fig. 1, *A*, *B*, and *C*, Table I).

During the remaining fifteen months covered by this study an additional three cases with complete division of the ulnar nerve in the elbow region or above and with good function of the small muscles of the hand were found. Cases 1, 2, and 3 were secondary to war wounds. Case 4 was of different etiology.

TABLE I (CASE 1). VOLUNTARY AND FARADIC RESPONSE RECORDED ON ALL MUSCLES*

DATE	1/3/45		4/12/45		5/9/45		8/10/45		11/13/45	
	PREOP.		POSTOP.		POSTOP.		POSTOP.		POSTOP.	
ULNAR NERVE	VOL	EL	VOL	EL	VOL	EL	VOL	EL	VOL	EL
Flexor carpi ulnaris	3	F	3	F	3	F	3	F	4	F
Flexor digitorum profundus 4	2	F	1	F	2	F	2	F	3	F
Flexor digitorum profundus 5	2	F	1	F	2	F	2	F	3	F
Abductor digiti quinti	2	F	2	F	3	F	3	F	3	F
Opponens digiti quinti	2	F	2	F	3	F	3	F	3	F
Dorsal interosseous 1	2	F	2	F	3	F	3	F	3	F
Dorsal interosseous 2	1	F	2	F	3	F	3	F	3	F
Dorsal interosseous 3	1	F	2	F	3	F	3	F	3	F
Dorsal interosseous 4	1	F	2	F	3	F	3	F	3	F
Palmar interosseous 1	2	F	2	F	3	F	3	F	3	F
Palmar interosseous 2	1	F	2	F	3	F	3	F	3	F
Palmar interosseous 3	1	F	2	F	2	F	3	F	3	F
Adductor pollicis	2	F	2	F	3	F	3	F	3	F
Sensory	A		A		A		A		H & A	

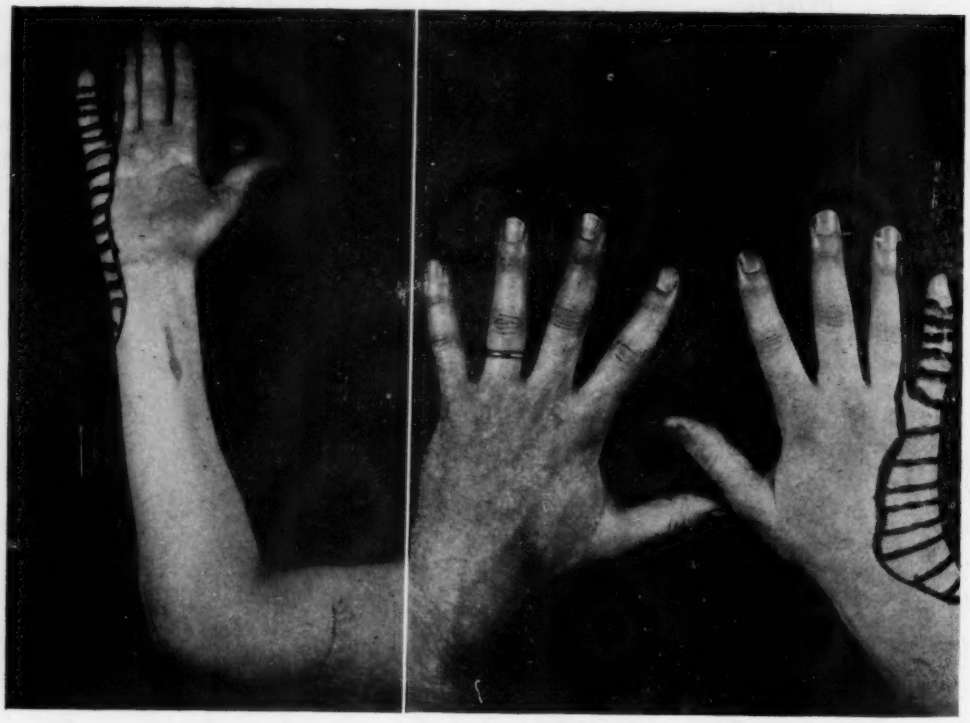
*Note the moderate improvement in function postoperatively. Sensation beginning to return only on last test.

CASE 2.—This soldier received a severe penetrating shell fragment wound, Oct. 7, 1944. The fragment entered the medial part of the arm 7 cm. above the condyle and lodged in the anterior part of the forearm 8 cm. above the wrist joint. He was first examined in the nerve laboratory, Wakeman General Hospital, Feb. 15, 1945. Because of a trigger point in the wound, anesthesia in the ulnar distribution, and failure of the Tinel sign to advance, exploration was carried out March 14, 1945. The nerve was found completely divided except

TABLE II (CASE 2). SLUGGISH RESPONSE TO FARADIC CURRENT*

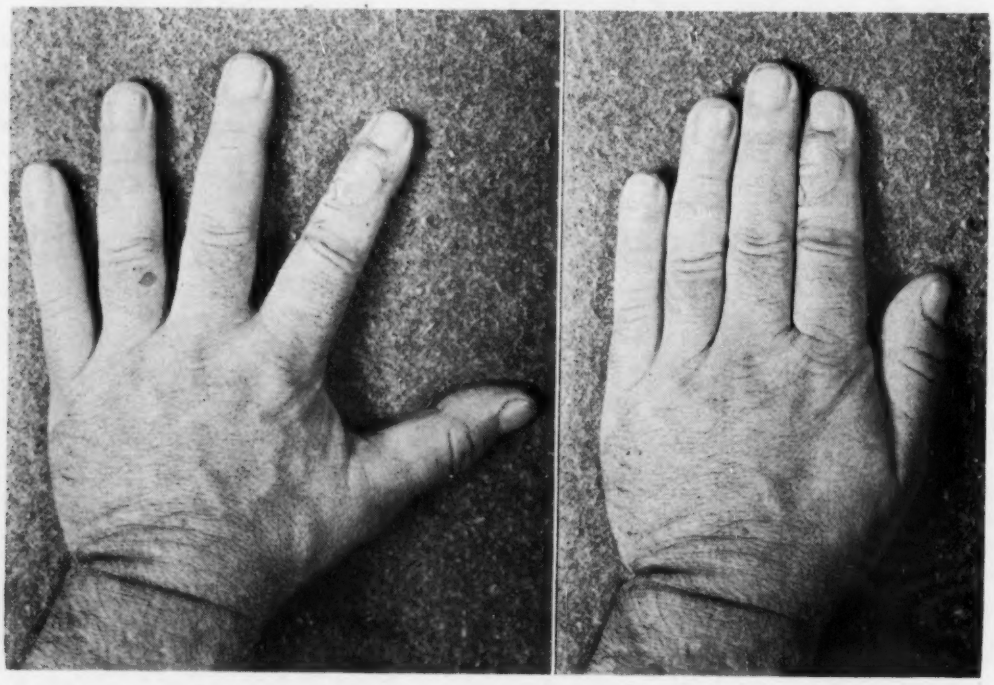
DATE	21/15/45		4/9/45		6/7/45		8/11/45	
	PREOP.		POSTOP.		POSTOP.		POSTOP.	
ULNAR NERVE	VOL	EL	VOL	EL	VOL	EL	VOL	EL
Flexor carpi ulnaris	3	F	3	F	3	F	3	F
Flexor digitorum profundus 4	2	F*	2	F	3	F	3	F
Flexor digitorum profundus 5	1	F*	2	F	2	F	3	F
							3	F
Abductor digiti quinti	2	F*	2	F	2	F		
Opponens digiti quinti	1	F*	2	F	2	F	3	F
Dorsal interosseous 1	2	F	2	F	3	F	3	F
Dorsal interosseous 2	2	F	2	F	3	F	3	F
Dorsal interosseous 3	2	F	2	F	3	F	3	F
Dorsal interosseous 4	2	F	2	F	3	F	3	F
Palmar interosseous 1	2	F	2	F	3	F	3	F
Palmar interosseous 2	2	F	2	F	3	F	3	F
Palmar interosseous 3	2	F	2	F	3	F	3	F
Adductor pollicis	3	F	3	F	3	F	3	F
Sensory	A		A		A		A	

*Note the good voluntary function throughout. Sluggish response to Faradic current on the first examination is indicated by the asterisks. Anesthesia throughout.



A. *B.*

Fig. 2.—*A*, Area of anesthesia outlined. Note the scar of the recent operation, three weeks postoperatively. Also note the scar of exit of the shell fragment. Note lack of ulnar Griffe. *B*, Note lack of atrophy, ability to spread fingers and area of anesthesia, postoperatively.



A. *B.*

Fig. 3.—*A* and *B*, Postoperative photographs (six weeks) without anesthesia outlined. Note ability to spread and approximate fingers and complete lack of atrophy.

for a band of scar tissue. Stimulation of the median nerve gave contraction of some of the small hand muscles of the ulnar nerve. Stimulation of the ulnar nerve above and below the neuroma failed to give any contraction of these muscles. Neurorrhaphy was performed after resection of the neuromas. Function remained after operation. Improvement gradually ensued and the final note, Sept. 5, 1945, stated, "Practically normal motor function. Sensory loss limited to distal two phalanges of 5th finger. Patient has been recommended for C.D.D." (J. R. R.) (Fig. 2, *A* and *B*, Table II.)

CASE 3.—This soldier received a perforating wound, the entrance in the postero-lateral part of the arm 6 cm. above the condyles, the exit in the medial part of the arm 8 cm. above the condyles, with associated fracture of the humerus, caused by a rifle bullet on Nov. 3, 1944. At débridement fourteen hours after injury it was noted that the ulnar nerve was lacerated. When seen first in the nerve laboratory at Wakeman General Hospital, April 8, 1945, he was found to have questionable function of the small muscles of the hand, with definite function of the first interossei, palmar and dorsal, and definite function of the adductor of the thumb. In view of the statement that the ulnar nerve was completely divided, it was felt most certain that this function was due to innervation through the median nerve. A recheck on April 23 gave the result shown in Table III. At operation, April 25, 1945, the nerve was found to be completely divided, the tips of the neuromas being separated by 4 cm. Three centimeters of neuroma were excised and a neurorrhaphy was performed with silk technique after transplanting the nerve. The patient had such good function three months after operation that the chief of section without knowledge of his status asserted, "The paralysis of the ulnar nerve has shown satisfactory recovery and all muscles show gross response and the area of the hypesthesia has diminished." He was separated from the service at this time (Table III).

TABLE III (CASE 3). MINIMAL FUNCTION OF SEVERAL MUSCLES TO VOLUNTARY TESTS*

DATE	4/23/45		5/28/45		7/23/45	
	PREOP.		POSTOP.		POSTOP.	
ULNAR NERVE	VOL	EL	VOL	EL	VOL	EL
Flexor carpi ulnaris	2	F	2	F	2	F
Flexor digitorum profundus 4	2	F	2	F	2	F
Flexor digitorum profundus 5	2	F	2	F	2	F
Abductor digiti quinti	0	F	?	F	1	F
Opponens digiti quinti	0	F	1	F	1	F
Dorsal interosseous 1	2	F	3	F	3	F
Dorsal interosseous 2	2	F	2	F	2	F
Dorsal interosseous 3	1	F	1	F	2	F
Dorsal interosseous 4	0	F	1	F	1	F
Palmar interosseous 1	1	F	2	F	2	F
Palmar interosseous 2	1	F	1	F	1	F
Palmar interosseous 3	1	F	1	F	1	F
Adductor pollicis	2	F	2	F	2	F
Sensory	A		A		H	T35

*However all respond to Faradic current.

CASE 4.—A 40-year-old Staff Sergeant was admitted on the General Surgery Section, Wakeman General Hospital, for treatment of a mass in the axilla. At operation, June 2, 1945, the tumor mass (6 by 3 cm.) was found to arise from the ulnar nerve and a neurosurgeon was called. He excised the tumor and did a neurorrhaphy. Twenty-eight days after operation, at examination in the nerve laboratory, the patient was found to have anesthesia in an ulnar distribution smaller than usual, but fair to good function of all ulnar muscles. Strangely enough, the flexor profundus 4 and 5 along with the abductor digiti quinti and the opponens digiti quinti were relatively the weakest (see Table IV). There were no other sensory changes. He was discharged Oct. 5, 1945, with function still present. The Tinel sign had advanced only 30 cm., or to the elbow (Fig. 3, *A* and *B*, Table IV).

All four of these patients with complete division of the ulnar nerve showed fair to good function of most of the ulnar nerve hand muscles, with little atrophy

TABLE IV (CASE 4). POSTOPERATIVE EXAMINATION*

ULNAR NERVE	DATE	6/30/45 POSTOP. VOL	6/30/45 POSTOP. EL	9/30/45 POSTOP. VOL	9/30/45 POSTOP. EL
Flexor carpi ulnaris		3	F	4	F
Flexor digitorum profundus 4		2	F	1	F
Flexor digitorum profundus 5		2	F	2	F
Abductor digiti quinti		1	F	3	F
Opponens digiti quinti		2	F	3	F
Dorsal interosseous 1		3	F	3	F
Dorsal interosseous 2		2	F	3	F
Dorsal interosseous 3		2	F	3	F
Dorsal interosseous 4		2	F	3	F
Palmar interosseous 1		3	F	3	F
Palmar interosseous 2		2	F	3	F
Palmar interosseous 3		2	F	3	F
Adductor pollicis		3	F	3	F
Sensory		A		A	

*No preoperative tests because lesion not suspected. Note anesthesia.

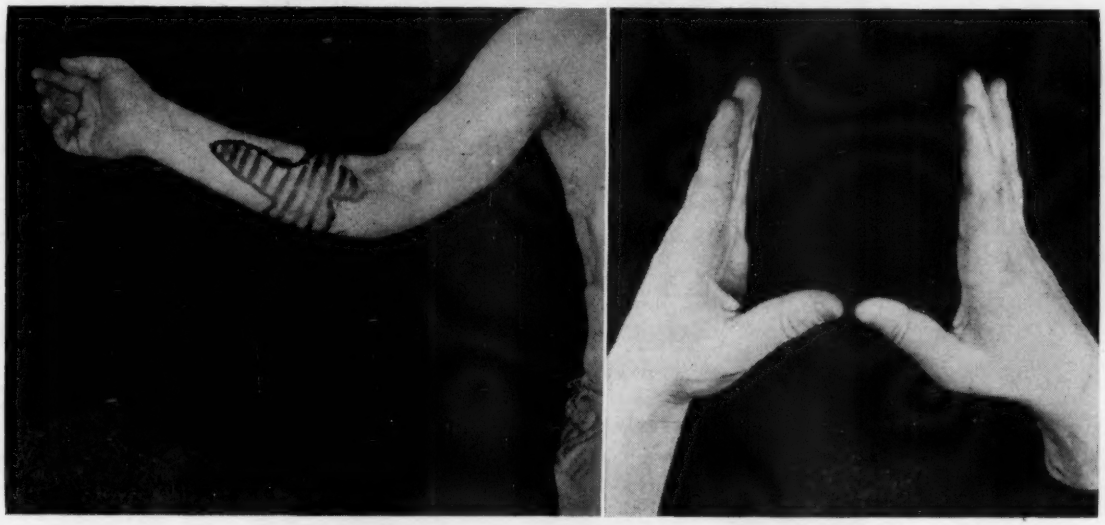
and the usual anesthetic area. This is significant in Case 4 since it might be considered that one of the sensory nerves was involved rather than the ulnar, as we first suspected in Case 1. This condition remained postoperatively despite known complete division of the nerve. In one patient, Case 1, a branch from the median nerve was proved to carry at least some of this function. In another patient, Case 2, stimulation of the median nerve in the upper arm gave contraction of some of the ulnar muscles, showing that the functioning elements were carried in this nerve in the area of operation.

At least three other cases of severance of the ulnar nerve without intrinsic muscle paralysis have been reported. All of these were cases of tumor similar to our Case 4. In Goldman's[6] case, a tumor and 5 cm. of the ulnar nerve were removed from above the elbow without any disturbance in motility of the hand or fingers. Auerbach and Brodnitz[7] found no paralysis in the ulnar distribution after complete section of the ulnar nerve above the elbow, for excision of a nerve tumor. Halipré[8] also found no motor loss after complete severance of the ulnar nerve in his case. In addition, at the time of operation he stimulated both cut ends of the nerve without any motor response. However, stimulation lower on the ulnar nerve did give contraction of the small hand muscles. During transfer procedures from Wakeman General Hospital the records of one other case were lost. This man was one of the original cases presented at the Wakeman General Hospital conference.

The first case reported here of function of median nerve muscles despite complete section of the nerve was also found purely by chance.

CASE 5.—This soldier suffered a guttering wound of the anticubital space and the adjacent arm on Aug. 10, 1944. The wound was covered by a pedicle graft measuring 11 by 6 cm. which had been applied on Sept. 1 and Oct. 6, 1944. He was sent to neurosurgery from the orthopedic section for consultation, Feb. 16, 1945, because of severe pain with use of an extension cast to correct the flexion deformity of the elbow. The patient was checked in the nerve laboratory and on examination he was found to have function of all the median nerve muscles except the flexor digitorum profundus of the index finger and the flexor pollicis longus. There was normal sensation in the median nerve distribution. There was a trigger

point, marked, over the median nerve in the elbow region at the lower edge of the graft. Pressure on this trigger area or extension at the elbow, beyond 120 degrees, resulted in severe pain and paresthesia along the course of the median nerve and in its sensory area. There was, in addition, marked tissue loss in the wound area and the biceps muscle tendon had been completely divided with much loss of substance. Flexion at the elbow was carried out by the brachioradialis muscle. At operation, March 7, 1945, the nerve was found to be divided except for a thin scar tissue bridge with the neuromas separated by 3.5 cm. The

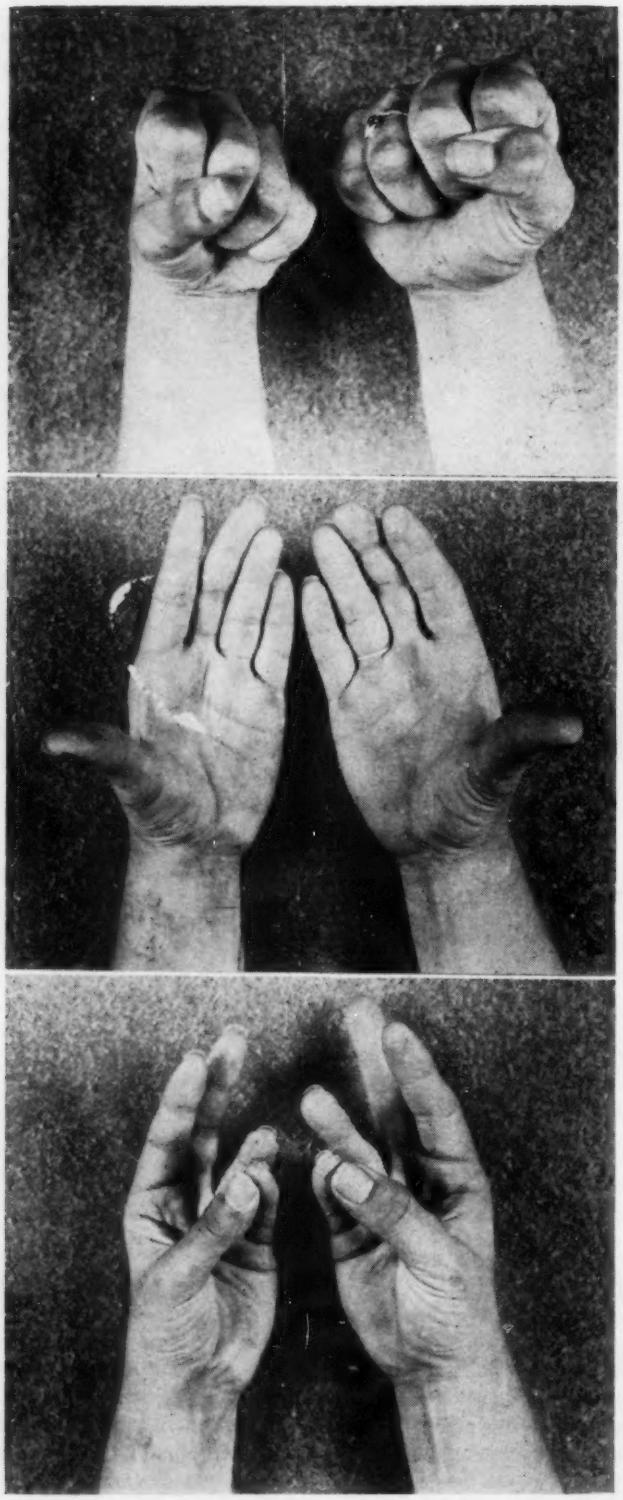


A. *B.*

C.

Fig. 4.—*A*, Note large wound covered by skin graft and area of anesthesia. *B*, Postoperative action photograph to show function abductor pollicis brevis. Note moderate atrophy of right thenar eminence. *C*, Postoperative photograph to show function of median muscles.

proximal neuroma was exquisitely tender. An additional 4 cm. of neuroma were removed and neurorrhaphy was performed using silk. One month postoperative he had the same function as before operation. By three months after operation there was return of function of the flexor profundus to the index finger. Hypesthesia of the distal two phalanges of the second and third fingers was noted at this time. The patient was discharged on Dec. 11, 1945, with function of all median muscles although the small thumb muscles were weak and the function of the flexor pollicis longus was questionable. He also had normal extension of the elbow without pain or paresthesia (Fig. 4, *A*, *B*, and *C*).



A.

B.

C.

Fig. 5.—*A*, Photograph to show function of median muscles. Note poor function of flexor pollicis longus. *B*, Photograph to show function of abductor pollicis brevis. This is imperfect in that there is too much associated extension of thumb. *C*, Photograph to show function of opponens pollicis. Note lack of atrophy.

TABLE V (CASE 6). DECREASE IN FUNCTION OF THE FLEXOR POLLICIS LONGUS, FLEXOR DIGITORUM PROFUNDUS 2, AND FLEXOR POLLICIS BREVIS*

DATE	7/10/45		8/17/45		9/27/45		11/27/45		12/20/45	
	PREOP.		POSTOP. 1 PREOP. 2		POSTOP. 2		POSTOP. 2		POSTOP. 2	
MEDIAN NERVE	VOL	EL	VOL	EL	VOL	EL	VOL	EL	VOL	EL
Pronator teres	3	F	3	F	4	F	4	F	4	F
Flexor carpi radialis	3	F	3	F	4	F	4	F	4	F
Flexor digitorum sublimus	3	F	4	F	4	F	4	F	4	F
Flexor digitorum profundus 2	3	F	1	F	2	F	3	F	3	F
Flexor digitorum profundus 3	3	F	3	F	3	F	4	F	4	F
Flexor pollicis longus	3	F	1	F	2	G3	3	F	3	F
Opponens pollicis	3	F	4	F*	4	F	4	F	4	F
Abductor pollicis brevis	3	F	3	F	3	F	4	F	4	F
Flexor pollicis brevis	3	F	3	F*	3	F	4	F	4	F
Sensory	A		A		A		A fingers H palm		A index and thumb H remainder	

*After the first operation; note rapid return postoperatively.

CASE 6.—This soldier received a moderate guttering wound of the palmar surface of the right forearm 9 cm. above the tip of the radius, Dec. 19, 1944. There was an associated severe laceration of the radial artery. Débridement and ligation of the radial artery and repair of a sensory branch of the radial nerve were performed seven hours after injury. A secondary closure and skin graft were performed, Jan. 27, 1945. The soldier was examined first in the nerve laboratory, March 28, 1945, two days after admission to Wakeman General Hospital. He was found to have anesthesia in the radial distribution. There was also anesthesia in the median distribution but no motor dysfunction. Because of a persistent trigger point in the wound over the median nerve, and the anesthesia, exploration was considered justified. It was our feeling that a neuroma would be found and that a neurolysis would be indicated. Much to our surprise at operation, July 17, 1945, the median nerve was found to be completely divided with a gap of 6 cm. and a large neuroma and glioma. One centimeter was removed from each end and a first stage neurorrhaphy performed with 000 silk sutures in the sheath. A secondary neurorrhaphy was performed, Aug. 27, 1945, by another operator. There was decreased function of the flexor profundus 2 and the flexor pollicis longus after the first operation, as indicated in the photograph of the fist (Fig. 5, *A*), but this function returned rapidly after the second operation. The patient was discharged, Dec. 29, 1945, still with good motor function and a decrease in the area of anesthesia, which now included only the index finger and thumb (Fig. 5, *A*, *B*, and *C*, Table V).

TABLE VI (CASE 7). LOSS OF FARADIC RESPONSE AFTER SECOND OPERATION

DATE	6/7/45		7/24/45		8/25/45		10/12/45		12/17/45		1/12/45	
	PREOP.		PREOP.		POSTOP. 1 PREOP. 2		POSTOP. 2		POSTOP. 2		POSTOP. 2	
MEDIAN NERVE	VOL	EL	VOL	EL	VOL	EL	VOL	EL	VOL	EL	VOL	EL
Pronator teres	3	F	3	F	3	F	–	F	3	F	3	F
Flexor carpi radialis	3	F	3	F	3	F	2	F	2-3	F	3	F
Flexor digitorum sublimus	3	F	3	F	3	F	2-3	F	3	F	3	F
Flexor digitorum profundus 2	3	F	3	F	3	F	2	F	3	F	3	F
Flexor digitorum profundus 3	3	F	3	F	3	F	3	F	3	F	3	F
Flexor pollicis longus	3	F	3	F	3	F	1	G3	3	G3	3	F
Opponens pollicis	3	F	3	F	3	G3	2	G3	3	F	3	F
Abductor pollicis brevis	3	F	3	F	3	G3	1-2	G3	2-3	G3	2-3	F
Flexor pollicis brevis	3	F	3	F	2	G3	0-1	G3	2-3	G3	2-3	F
Sensory												

CASE 7.—On New Guinea in early 1944, this soldier developed symptoms of a painful tumor of the hand. On April 26, 1944, at the 116th Station Hospital, it was excised and found to be a neuroma of the median nerve. He was first examined in the nerve laboratory at Wakeman General Hospital, June 7, 1945, at which time it was noted that he had anesthesia in most of the median nerve distribution, but almost normal motor function. A

A. *B.*

C.

Fig. 6.—*A*, Photograph showing abductor pollicis brevis function. *B*, Photograph showing opponens pollicis function. Note lack of atrophy. *C*, Hand and forearm postoperatively, showing operative incision and lack of atrophy of thenar muscles.

tender mass was palpable just above the wrist, palpation of which caused paresthesia in the second and third fingers. At exploration, Aug. 1, 1945, the median nerve was found to be completely divided and the proximal end had retracted to above the wrist. After excision, for biopsy, the nerve was drawn down to the transverse carpal ligament by tension sutures. The pathologic report was benign neuroma. There was temporary decrease in function of the thumb muscles three weeks postoperatively, as recorded (Table VI). This was evidently due to the operative trauma in the region of the thenar eminence. At a third operation, Sept. 17, 1945, a neurorrhaphy was performed with marked tension despite transplantation anterior to the pronator muscle. Function was poor four weeks after this operation, but rapidly returned to the preoperative level three and four months after operation. There was, by this time, return of sensation except for the distal phalanges of fingers 2 and 3. He was discharged on Jan. 12, 1946 (Fig. 6, *A*, *B*, and *C*, Table VI).

Fig. 7.—Photograph to show scar of wound and area of anesthesia. Note minimal thenar atrophy.

CASE 8.—This soldier received a moderate perforating wound, from the posterolateral to the anterior part of the forearm, 4 cm. below the condyles, June 14, 1944. This was associated with complete, comminuted fracture of the radius. When first examined in the nerve laboratory, April 2, 1945, he had function of all median muscles, although several failed to respond to faradic current. There was anesthesia in the median distribution, plus a trigger point in the scar, for which operation was considered necessary. A neuroma was expected. At operation, May 7, 1945, a large neuroma 9 by 3 cm. was found, excised, and neurorrhaphy performed. The postoperative nerve laboratory examination showed function of all median muscles which persisted except for the flexor pollicis longus, function of which was lost after three months. There was gradual return of sensation until discharge, Feb. 1, 1946, when, only the fingers were still anesthetic (Fig. 7).

CASE 9.—This soldier received a perforating wound through the forearm from the posterior to the anterior part, 5 cm. above the wrist on July 3, 1944. Débridement was done thirty hours later. A preoperative examination was not made in the nerve laboratory,

but the preoperative test by the operating neurosurgeon revealed function of all median muscles, with anesthesia in the median distribution and a trigger point in the wound. At operation, Dec. 7, 1944, a hard neuroma was found. Stimulation above and below the neuroma gave no contraction of the thumb muscles. Excision of the neuroma and neurorrhaphy were carried out. At the first examination in the nerve laboratory, one month postoperatively, there was decrease in function of the abductor pollicis brevis, but no other change in motor function or sensation. Through the postoperative course there was gradual, slow improvement in function until nine months postoperative, when all muscles functioned well and there was return of sensation except for the tip of the index finger (Table VII).

TABLE VII (CASE 9). LACK OF FARADIC RESPONSE OF OPPONENS AT SIX AND NINE MONTHS*

DATE			3/8/45		6/2/45		9/10/45	
	PREOP.		POSTOP.		POSTOP.		POSTOP.	
MEDIAN NERVE	VOL	EL	VOL	EL	VOL	EL	VOL	EL
Pronator teres	4		4		4	F	4	F
Flexor carpi radialis	4		4		4	F	4	F
Flexor digitorum sublimus	4		4		4	F	4	F
Flexor digitorum profundus 2	4		4		4	F	4	F
Flexor digitorum profundus 3	4		4		4	F	4	F
Flexor pollicis longus	4		4	G3	4	F	4	F
Opponens pollicis	3		3	F	3	G3	4	G3
Abductor pollicis brevis	2		1	F	3	F	3	F
Flexor pollicis brevis	4		3	F	3	F	4	F
Sensory	A		A		A fingers		A fingertips	

*Otherwise, function throughout. No electrical tests preoperatively as this examination was not done in nerve laboratory.

CASE 10.—This soldier received two penetrating wounds of the right upper extremity, Dec. 14, 1944. He was first seen in the nerve laboratory, Wakeman General Hospital, on March 2, 1945. It was noted at that time that he had marked limitation of motion of the elbow. With extension to 110 degrees he had severe pain in the wound area with radiation through the course of the median nerve into the median nerve distribution of the hand. There had been return of function of all median muscles except the flexor pollicis longus, but anesthesia was present throughout the median distribution. It was thought that perhaps a foreign body pressed on the nerve, causing the symptoms and signs indicated. The patient was continued on physiotherapy without improvement and operation was performed on July 4, 1945. The branches to the forearm muscles were scarred, but the main trunk was almost completely divided. No stimulator was available for tests. A neurorrhaphy was performed on the main trunk. At examination, one month postoperatively, he was found to have the same function as before operation and in addition the Tinel sign also remained at 20+ cm. as before operation. Six months postoperatively, there was beginning return of function of the flexor pollicis longus and by the time of discharge, one year postoperatively, there was sensation, although far from normal, present throughout the median distribution. The foreign body was removed, Feb. 21, 1946, because of a persistent draining sinus through the wound.

These six patients with median nerve injury examined pre- and postoperatively all showed function of the thumb muscles, according to the usual criteria. Unfortunately, neither the ulnar nor the musculocutaneous nerves were stimulated in any of these cases.

The cases to follow show the possibility of considering good function as an operative result rather than realizing that the function was present before operation. Some of these cases are from the Wakeman General Hospital and we have definite proof from the records. Others are from other hospitals, about

which there may be some question. However, no case had been considered without definitely recorded objective tests, usually the physiotherapists, from other institutions.

CASE 11.—This soldier received a penetrating, severe wound of the axilla and shoulder region on July 3, 1944. Diagnosis was severe brachial plexus injury with complete musculocutaneous and ulnar nerve paralysis and partial radial and median nerve paralysis. At operation on Nov. 16, 1944, the ulnar nerve was found to be completely separated by 5 cm., and a neurorrhaphy under tension was performed using tantalum wire stay and epineural sutures. The radial nerve was partially divided and a partial neurorrhaphy was performed. Neurolysis was done on the median and musculocutaneous nerves, because there was contraction of the muscles when the median and musculocutaneous nerves were stimulated. There was no function with ulnar or radial nerve stimulation. It was a complete surprise to find voluntary function of some, and faradic response of all, ulnar small hand muscles six weeks after operation. Three months postoperatively, there was function of all ulnar muscles, but still complete ulnar anesthesia. It was at this point that the entire record was carefully re-examined and we found that the last examiner, one week before operation, had observed beginning function of some of the ulnar muscles. These records are not available for reproduction.

If this return of function had been delayed longer there is little question that this return would have been claimed as an operative result.

CASE 12.—This soldier was wounded on Dec. 31, 1944. On March 29, 1945, a neurorrhaphy of the median nerve, 5 inches above the wrist, was performed in an overseas hospital. On examination in the nerve laboratory, July 17, 1945, he was found to have some function of all median muscles except the abductor pollicis brevis. This was considered a possible return of function until his overseas records were checked and it was found that he had had good to normal function of median muscles sixteen days before operation. Two months after operation another observer had noted that he showed return of function of all median muscles, but still had complete anesthesia. By failure to check the preoperative records this would have been considered a return of function through regrowth of the nerve (Table VIII).

TABLE VIII (CASE 12). PREOPERATIVE RECORDINGS COPIED FROM THE RECORDS OF 67TH GENERAL HOSPITAL*

DATE	3/13/45		7/17/45		9/19/45	
	PREOP.		POSTOP.		POSTOP.	
MEDIAN NERVE	VOL	EL	VOL	EL	VOL	EL
Pronator teres	N	F	2	F	4	F
Flexor carpi radialis	G	F	2	F	2	F
Flexor digitorum sublimus	N	F	2	F	2	F
Flexor digitorum profundus 2	N	F	1	G3	0-1	G3
Flexor digitorum profundus 3	N	F	2	G3	0-1	F
Flexor pollicis longus	N	F	2	F	2	F
Opponens pollicis	N	F	1	F	2	F
Abductor pollicis brevis	N	F	2	G3	3	F
Flexor pollicis brevis	G	F	0	G3	1	G3
Sensory	A		A		A	

*Recordings are shown as N, normal and G, good, rather than 1, 2, 3, and 4. Postoperative function was not so good as preoperative function if this is accurate.

CASE 13.—This soldier was wounded in action on Aug. 6, 1944. Operation was performed on March 13, 1945, at another general hospital, when the median nerve was found to be completely separated and a neurorrhaphy was performed. The patient was transferred to Wakeman Convalescent Hospital with a report (on Surgeon General form 941) of returning function of the median nerve. However, this would be virtually impossible since the lesion was in the mid-upper arm, 50 cm. from the hand. On careful examination of the previous records it was noted that he had had definite function before operation.

CASE 14.—This soldier who was wounded Sept. 24, 1944, had a neurorrhaphy of the median nerve performed at another general hospital on Jan. 25, 1945. When he was found to have function four months after operation, he was considered to be showing return of function. However, on careful examination of the records, a physiotherapy record at one month postoperatively was found, which showed function of all median nerve muscles. Since this would be too early for return of function after operation, one must consider that he also had function before operation.

The last patient (Case 15), although possibly belonging with Cases 5 to 10, is considered separately because he was returned to duty without operation from another neurosurgical hospital.

CASE 15.—This soldier received a lacerating wound of the volar aspect of the wrist on Dec. 12, 1944. After healing of the wound he was returned to duty from a general hospital with a neurosurgical service and did full duty until he was returned to the Zone of Interior for separation. He was seen in consultation from the separation center on March 12, 1946. He had anesthesia in the median distribution, but good motor function. Admission and exploration were advised. At exploration, March 20, 1946, the nerve was found to be completely divided with a gap of 1½ cm. between the tips of the neuroma and glioma. Stimulation of the median nerve before and after dissection gave no contraction of the opponens pollicis, flexor pollicis brevis, or abductor pollicis brevis. Stimulation of the ulnar nerve gave good contraction of the thumb muscles. After the dissection, however, as the glioma was excised from the distal end of the median nerve, the patient complained of pain in the exact median nerve distribution and electrical stimulation of the distal end of the nerve gave the same reaction, that is, pain in the median distribution. Postoperatively, excellent function remained. He had very slow return of sensation in the median distribution and by Oct. 24, 1946, he had return of pain and touch sensation except in the distal two phalanges of the second and third fingers (Table IX).

TABLE IX (CASE 15). EXCELLENT FUNCTION OF ALL MUSCLES WITH ANESTHESIA

DATE	3/12/46		4/11/46		6/24/46		8/27/46		10/24/46	
	PREOP.		POSTOP.		POSTOP.		POSTOP.		POSTOP.	
MEDIAN NERVE	VOL	EL	VOL	EL	VOL	EL	VOL	EL	VOL	EL
Pronator teres	4	F	4	F	4	F	4	F	4	F
Flexor carpi radialis	4	F	4	F	4	F	4	F	4	F
Flexor digitorum sublimus	4	F	3-4	F	3	F	3	F	3	F
Flexor digitorum profundus 2	4	F	3	F	3	F	3	F	3	F
Flexor digitorum profundus 3	4	F	3-4	F	3	F	3	F	3	F
Flexor pollicis longus	4	F	3-4	F	3	F	3	F	3	F
Opponens pollicis	4	F	4	F	3	F	3	F	3	F
Abductor pollicis brevis	4	F	3-4	F	3	F	3	F	3	F
Flexor pollicis brevis	4	F	4	F	3	F	3	F	3	F
Sensory	A		A		A		H palm A fingers		H all but distal 2 & 3 fingers	

This last case (Case 15) revealed another interesting phenomenon which was found on at least five median nerve cases during operation with local anesthesia. Stimulation either by grasping or by the stimulator current, of the distal end of the completely divided nerve gave a painful sensation in the area of distribution of the median nerve. All of these injuries were in the lower forearm. We failed to make the obvious test of blocking the ulnar and radial nerves

to determine which carried the pain impulses to the central nervous system. One other possibility would seem to be the periarterial sympathetics. As far as is known this phenomenon did not occur on any nerves other than the median.

DISCUSSION

If one can confirm function of muscles which are usually innervated through an already divided or seriously damaged nerve, as in these cases, an anomalous innervation must be considered. Further proof can sometimes be produced by stimulation or block of the nerve which is supposed to carry the anomalous or unusual nerve fibers. These unusual innervations are of great importance in primary diagnosis and planned treatment of nerve injuries and of especial importance in judging the recovery following repair of nerves. If care is not taken in determining preoperative function of these muscles by careful tests, one may be led to claim a good result from nerve repair on the basis of the usual innervation when the unusual innervation is the true cause of the good function. This would be more likely to occur in cases with temporary paralysis of the second nerve and return of function between examinations. Several of the cases reported show clearly these pitfalls in determining return of motor function.

As far as the original diagnosis is concerned one may be led to accept a partial function of muscles to mean only slight damage to the nerve and thus to procrastinate, expecting further return of motor function and sensation. Such is Case 15. In many cases undoubtedly these patients have been discharged with the assurance that there would be rapid continued return of function. Certainly this was almost done in several of these cases and it was done in one shortly after operation (Case 3).

If we are going to accept this unusual condition, even as a possibility, we must first establish the fact that there are nerve pathways other than the so-called normal pathways over which the stimuli may be carried. Fortunately several of the older anatomists have by their evident tedious and careful work furnished us with the proof of the presence of several such variations in the nerve pathways to the hand.

The explanation for the variations in these particular nerves lies in their embryology. In the human being there are three nerves, median, ulnar, and musculocutaneous, serving one basic muscle group, the primitive ventral musculature of the arm. For the primitive dorsal musculature in contradistinction, there is just one nerve, the radial. Communicating fasciculi between the median and ulnar nerves and between the median and musculocutaneous nerves are not uncommon. A communication between the median and ulnar nerves was found in 38 of 125 cadavers by Gruber[9] and in 15 per cent of 406 cadavers by Thompson.[10] According to Piersol[11] such a communication is found in 20 to 25 per cent of cases.

The communications occur most frequently in the forearm as in Case 1, in a second case of the Wakeman General Hospital group not reported in this series,

and in one of the cases reported by Murphy and co-workers.[1] Thompson[10] described four specific types of communication:

(1) A communication arising from the anterior interosseous nerve about 5 cm. below its origin from the median which joined the ulnar nerve in its middle one-third passing below the ulnar artery upon the flexor digitorum profundus

(2) A branch from the main trunk of the median nerve joining the ulnar in the same manner as in (1)

(3) A sling communication occurring over the flexor digitorum profundus formed by both median and ulnar nerves, with branches from the sling supplying the flexor digitorum profundus to the fourth and fifth fingers

(4) A branch arising from the median nerve in the elbow region passing superficial to the flexor muscles and joining the ulnar nerve in its middle one-third

Borchardt and Wjasmenski[12] traced some of these communications more thoroughly and found that frequently the communicating branch divided into sensory and motor fibers. The sensory branch joined fibers in the ulnar nerve which supplied the skin on the inner part of the palm, over the palmaris brevis muscle, and the fourth and fifth fingers. The muscular branch joined that part of the ulnar nerve which supplied the intrinsic muscles of the hand.

Less commonly, communications between the median and ulnar nerves occur in the arm as high as the axilla. I visualized such communications in two cases.

Within the hand itself there are two communications of some importance. One is sensory for the adjacent surfaces of the third and fourth fingers. The other, described and illustrated best by Fröhse and Frankel,[13] is motor between the deep branch of the ulnar and the motor branch of the median, passing through the abductor pollicis brevis and along the flexor pollicis brevis. In Piersol's[11] text it was stated that the communications in the forearm are usually from median to ulnar, while in the hand they may be in either direction. Turner[14] went further and stated that the communication in the hand is usually from ulnar to median.

These facts would fit in with the finding that in no instance of division of the ulnar nerve below the upper forearm was definite function found of the ulnar intrinsics, except of the first interosseous in a few cases, whereas in the median nerve, function was found even with division at the wrist. As far as the first interosseous is concerned, it evidently occasionally receives twigs from the median nerve, as shown by Turner[14] and Mackenzie.[15] Communications between median and ulnar nerves have also been described in textbooks of anatomy by Cunningham,[16] McClellan,[17] Quain,[18] Toldt,[19] Verchere,[20] and Villar.[21]

The anatomic variations which might explain the residual function of the median nerve thumb muscles are even more varied than those of the ulnar nerve. In addition to the possible communications in the arm, forearm, and primarily in the hand between the ulnar and median nerves, there are variations in formation

of the median nerve and its relations to the musculocutaneous nerve. The two or more heads of the median nerve may unite as low as the elbow (Piersol[11]).

Communications between the median and musculocutaneous nerves are very common. In fact in some vertebrates, such as the ruminants, the median and musculocutaneous nerves are united in a single trunk. Some early anatomists including Hyrtl[22] considered the musculocutaneous to be a branch of the median nerve. Such an origin does occur but is unusual. The median nerve may take over some or even all of the musculocutaneous function. Much more rarely the musculocutaneous nerve may take over partly or completely the motor and sensory distribution of the median nerve (Gegenbauer,[23] Gruber,[24] and Krause[25]). According to Gegenbauer,[23] some form of communication may be found in 70 per cent of cases. The extent of communication between these two nerves may also vary somewhat according to the type of plexus. The passage is more commonly from the musculocutaneous to the median in the post-fixed plexus, and the reverse in the prefixed plexus. In the post-fixed plexus this communication from musculocutaneous to median is most likely to contain fibers from the fifth cervical root.

By finer dissection three general types of musculocutaneous to median fibers have been shown. In some instances all three types may be present in one communicating branch. Type 1 passes to the median nerve, runs in it for a short distance, and then returns to the musculocutaneous nerve. Type 2 enters the funiculus of the median nerve which is destined for the pronator teres and flexor carpi radialis and has been traced as far as the humeral head of the pronator teres. Type 3 divides into two branches, one entering a sensory path in the dorsal aspect of the nerve trunk; the other branch has been followed through the median nerve into the forearm where it communicates with the funiculus supplying the thenar muscles.

Variations in the median and musculocutaneous nerves have also been described by Piersol,[11] Borchardt and Wjasmenski,[12] Fröhse and Frankel,[13] Cunningham,[16] Quain,[18] Villar,[21] Testut,[26] and Cruveilhier.[27]

These variations in origin or communication with the musculocutaneous by the median nerve might well explain the result in Cases 5, 10, and 13, where the division of the median nerve was above the elbow. This is especially true of Case 10 where a Tinel sign to 20+ cm. below the point of division was present both pre- and postoperatively. Other possibilities in this case (Case 10) would be that fibers were carried through the branches to the forearm muscles rejoining the main trunk below the elbow or even a junction of heads of the median nerve below the elbow. Those patients with division in the forearm (Cases 8, 9, and 12) could have their innervation through branches in the forearm from the ulnar or from the anterior interosseous, or in the hand from the deep ulnar, as must have occurred in those with division at the wrist (Cases 7 and 15).

Those patients with pain on stimulation of the distal stumps of the median nerve can be explained only on the basis of communication with the central nervous system through some other nerve in the hand. This could be through the ulnar (Piersol,[11] Borchardt and Wjasmenski,[12] Fröhse and Frankel,[13] and McClellan,[17] the musculocutaneous, or the radial (Piersol,[11] Fröhse and

Frankel,[13] and Toldt[19]). Another possibility might be a communication through the periarterial sympathetics. The fact that the median nerve is the only nerve in which this phenomenon was noted and is the nerve in which causalgia is most common might make one consider this remote possibility.

The question may be asked, how do such small communicating branches produce such great function? It must be reiterated that function in these cases was not entirely normal, but ranged from fair to good. It is well known that there are intraneural plexuses with branches between the individual funiculi, in all nerves (Langley and Hashimoto[28]). It is not too difficult to suppose that these branching fibers may communicate with several funiculi by intraneural plexuses and, in fact, this has been shown by careful anatomic dissections. That two or three funiculi may carry some function to all muscles served by a given nerve was adequately proved by another patient treated at Wakeman General Hospital. This soldier, who had a thigh wound, had causalgia in the tibial distribution, but weak function of all tibial and peroneal muscles and some sensation throughout. At operation two intact funiculi of approximately eight present in the peroneal nerve were saved and three of the eight in the tibial nerve were saved. Stimulation above the area of injury after division of all but these intact funiculi gave some contraction of all muscles, and stimulation below gave not only the same motor function but also some pain sense. Dissection of these intact funiculi down into the distal nerve revealed several small fibrils passing from them into other funiculi which were divided proximally. These were evidently part of the intraneural plexus. A partial neurorrhaphy was performed leaving the intact funiculi. Some function was lost immediately postoperatively, but function had returned to almost the preoperative level by three months after operation.

The greater actual and relative number of median nerve cases is undoubtedly on the basis of the fact that it is so difficult to be sure of function of the small hand muscles served by the ulnar. Two questionable cases of the ulnar nerve were considered, but ruled out on the basis of uncertainty, and one certain case was lost. Function of the first interosseous has occurred in approximately 10 per cent of the cases of ulnar nerve division.

It was also observed in several of these cases that the relative size of the nerves was changed. Thus, in at least two of the median nerve cases the nerve looked much smaller than the normal median nerve, both proximally and distally, while the ulnar seemed larger than usual. The same relative change held true we believe in the reversed cases. No objective measurements were made.

CONCLUSIONS

1. Several cases of residual function of the small hand muscles, despite complete section of the nerve which usually supplies them, are reported.

2. Anatomic pathways (communications between the median and ulnar and median and musculocutaneous) for nerve impulses to these muscles are described.

3. These unusual cases are of importance in judging cases of peripheral nerve injury preoperatively and in evaluating return of function postoperatively.

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TANTALUM GAUZE IN THE REPAIR OF HERNIAS COMPLICATED BY TISSUE DEFICIENCY

A Preliminary Report

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THERE are many admirable methods of repairing the various hernial apertures of the body. Necessarily some of these procedures are better than others and, depending upon the situation which confronts the surgeon, one or the other of them may be the "best." The choice of herniorrhaphy must have basis: sound knowledge of the anatomy and physiologic requirements of the region; a recognition of the fundamental factors concerned in wound healing and tissue repair; and a certain ingenuity which allows an occasional disregard of "routine procedures." The skillful application of these factors to the requirements of the individual operation is of far more importance than certain technical knickknacks which are dignified by the term "modifications." In conformance with surgical principles, the operation must be made to fit the patient. Many unsatisfactory results are occasioned when standard procedures are attempted in unusual surgical situations.

Nowhere is this more apparent than in difficult herniorrhaphy. If the surgeon finds his repertoire exhausted, he must extemporize to meet the problem. The defect to be covered may be enormous; the structures may be attenuated and friable, and the whole inguinal canal may present such a wreck that the possibility of cure seems remote. It may seem quite impossible for *usual* methods to succeed. Thus, the surgeon is confronted with three possibilities: (1) as is commonly the case, he may resort to a policy of masterly inaction; (2) he may employ some hypertrophied variety of the primeval truss, with all its discomforts, uncleanliness, perennial adjustments, and eventual failure; (3) he may improvise some operative method which goes beyond the mere autoplastic aims of usual surgical repair. It is in this latter instance that the employment of tantalum gauze offers a useful adjunct to the performance of a difficult herniorrhaphy.

Tantalum gauze is a finely woven mesh of monofilament tantalum wire, 2 to 5 mils in diameter.* The finest weave, 100 by 100, resembles heavy sheer cloth. The weave more commonly used, 50 by 50, is a light pliable screen.† This material was first developed as a dressing for burns. Brief experience soon made it evident that it offered no advantages, and that it did make for certain disadvantages as compared to other materials available for that purpose. This has been confirmed by Lam.[4] However, the innate properties of tantalum, enhanced by

The materials for this work were furnished through the courtesy of the Ethicon Suture Laboratories, New Brunswick, N. J. It is a pleasure to acknowledge the aid of Mr. I. R. McCall in developing a tantalum gauze suitable for herniorrhaphy, and his help in metallurgical problems.

Received for publication, April 16, 1947.

*A mil is 0.001 of an inch, used as a measure of wire diameter. For example, 10 mil wire is B. and S. gauge 30, or 000 U.S.P. catgut size.

†Tantalum gauze is now available only as a 50 by 50 weave of 3 mil wire.

its employment as a fine mesh, prompted its use in the repair of large abdominal defects and particularly in difficult herniorrhaphy when the size or location of the defect seemed otherwise an almost insurmountable obstacle.

The relation of tantalum sutures and appliances to tissue repair is well known. Its position is that of a biologically inert foreign body. Tissue repair progresses rapidly and unimpeded in its presence, allowing nature to proceed in an orderly fashion and with a minimum of interference.

The use of metallic filigrees, grids, plates, and mesh is not new to the field of herniorrhaphy. Such appliances had some vogue at the turn of the century. Phelps[7] (1894) treated many inguinal hernias by placing coiled silver wire on the floor of the inguinal canal and approximating the layers of the abdominal wall over it. Witzel[8] (1900) constructed, in the tissues, a rude network of crossed silver wires and suggested to the surgical world the idea of embedding a ready-made filigree. Goepel[3] (1900) was the first to make use of such a ready-made filigree. Meyer[6] (1902) reported the use of a silver wire netting made up after the fashion of ordinary mosquito bar. Bartlett[1] (1903) introduced a filigree of wire loops, usually held in position by a central strand. These appliances were made of heavy silver wire. Many of them were so rigid that the discomfort of the patient dictated their subsequent removal. The sutures employed were also of silver wire, which frequently broke on the knot and became fugitive in the tissues. Wound infections occasionally developed and, with metallic implants in place, drainage was often prolonged—probably in many instances by the vigorous therapy directed toward the sinus tracts. However, eventual healing was the rule. Accurate statistics as to the operative results are not available; but it is evident that many hernias, otherwise considered inoperable, were cured. The practice gradually fell into disuse for three reasons: (1) Occasional discomfort experienced by the patient. McGavin[5] (1907) reporting on silver filigree herniorrhaphy, stated: "The greatest difficulty has been with rigidity. Pliability is necessary so that the implant shall at all times and in all positions yield to bodily movements. Most rigid gridirons, having a stout framework supporting a heavy wire trellis, were so uncomfortable that they had to be removed." (2) The fact that silver wire and appliances are ill-suited for tissue implantation, because they are not inert and because they rapidly work-harden. (3) A sentimental distrust of a foreign body in the tissues.

The tantalum mesh now in use, from the standpoint of both its innate properties and its physical fabrication, has little resemblance to the earlier filigrees except in its ultimate purpose (Fig. 1). It is strong, pliable, biologically inert in the tissues, and forms a scaffold for the ingrowth of sturdy white fibrous tissue which firmly closes the hernial defect. Its use is relatively simple when compared to many autoplastic procedures, and its adaptability to the various situations which arise during a difficult herniorrhaphy is satisfactory.

A hernia frequently is associated with a deficiency in fascial structures. When the proportions of the defect are such that the approximation of its edges is difficult or impossible, the logical mind searches for a suitable patch. The autoplastic procedures have run the gamut from the simple fascial flap or fascial

suture to periosteal flaps, free or pedicled fascial transplants, and dermis grafts. Certain of these methods, as the Gallie fascial suture, have enjoyed well-earned popularity; but when such a herniorrhaphy must be performed under tension, a recurrence follows. The extent to which various relaxing incisions or maneuvers may be helpful, each surgeon may readily determine for himself. Autoplastic procedures are valuable; they are often difficult, and they are far from uniformly successful under adverse conditions.

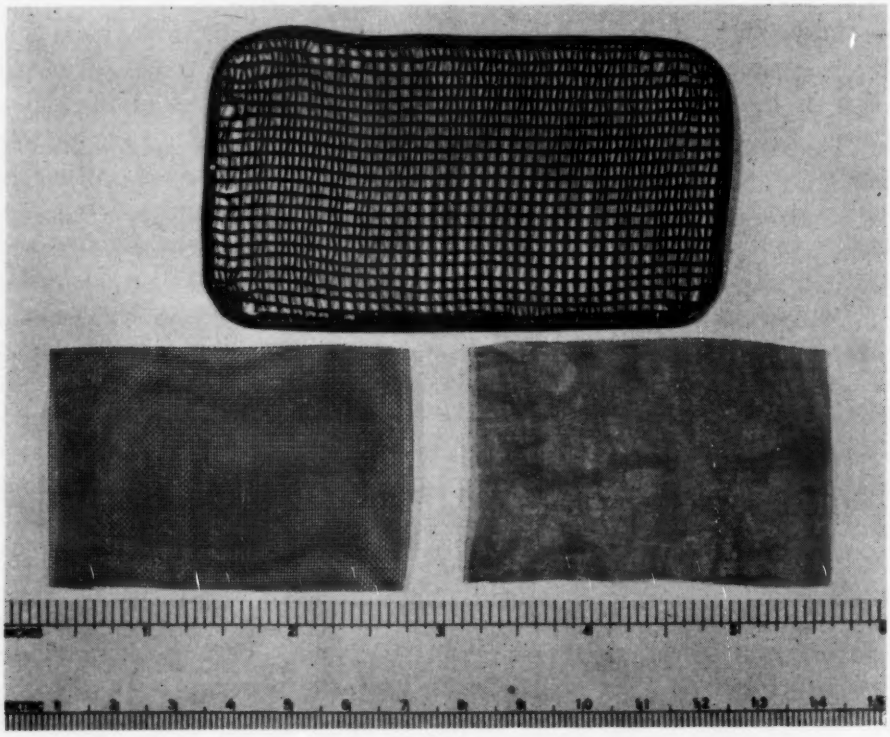

Fig. 1.—The difference in the silver wire screens used *circa* 1900 and the tantalum gauze used in this series of cases is shown. *Above* is a silver screen implanted by the late Dr. David S. Fairchild, Sr. of Clinton, Iowa, and which was subseuently removed because of ulceration and subjective discomfort. *Lower left* is the heaviest tantalum gauze used—a 50 by 50 weave of 5 mil wire. *Lower right* is the finest tantalum gauze used—a 100 by 100 weave of 2 mil wire.

THE TECHNIQUE OF TANTALUM GAUZE HERNIORRHAPHY

The technique of tantalum gauze herniorrhaphy is capable of almost unlimited modification to fit the individual situation. Such a mesh, together with its ensheathing white fibrous tissue, forms an impervious patch wherever the surgeon places it. In the continued use of this material, certain features have assumed increasing significance:

1. The cut edges of the implant should be folded under for approximately 1 cm. This serves the double purpose of creating a smooth, atraumatic edge, and also making it possible, when suturing the mesh in place, to pass all sutures through a tough, double thickness of material.

2. All sutures holding the implant in position should be placed in strong white fascia or periosteum and the dissection must expose these structures adequately. The dimensions of the implant are limited not by the size of the actual defect to be covered, but by the position of *reliable* supporting structures.
3. The implant must be of such generous proportions that it can be sutured in place *without tension*. More herniorrhaphies have been defeated by tension than by choice of suture material.

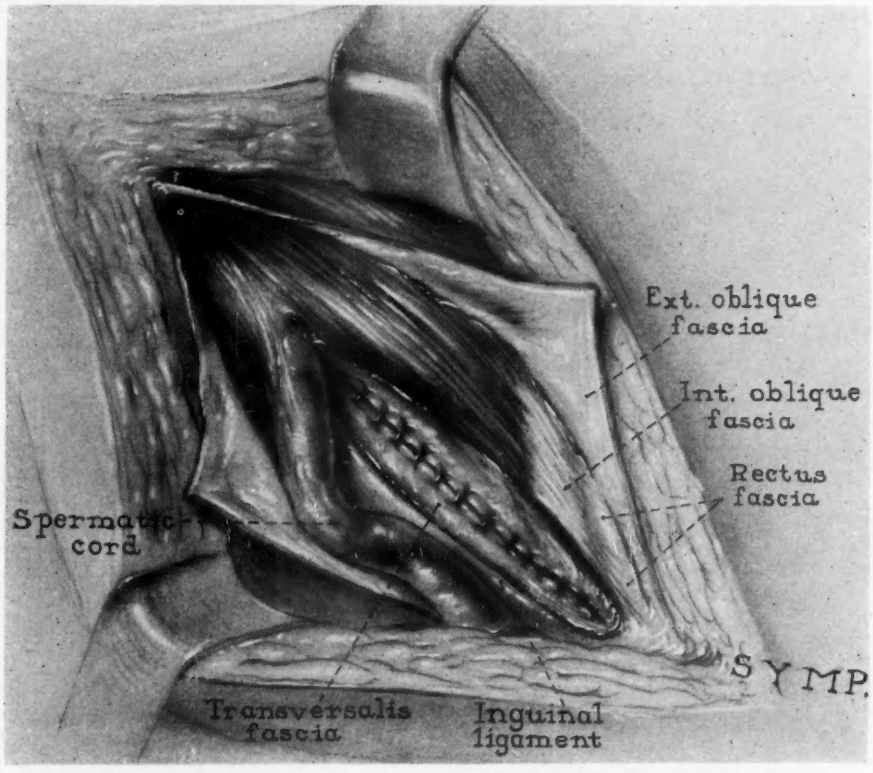

Fig. 2.—The inguinal canal is open; the direct hernial sac has been excised and the peritoneum closed. The rent in the transversalis fascia has been repaired with a row of interrupted sutures of 10 mil tantalum wire.

4. The suture material used to hold the tantalum gauze in place should be monofilament tantalum wire. The 10 mil size has seemed best suited to this purpose. The braided tantalum wire, although slightly easier to tie, was discarded because its finely serrated surface produced a notable "drag" when drawn through the screen. Other types of wire sutures were not used because of a difference in electrolytic potential between them and the gauze implant.
5. The wire sutures should be cut "on the knot." If unaccustomed to the use of metallic sutures, the surgeon may experience some initial difficulty with tantalum wire. A continuous type of suture should not be used. One-handed knots are not satisfactory. A simple

square knot should be tied, with only sufficient tension on the first throw to co-apt the structures being sutured. The second throw must lie flat and should be set snugly. The ends of the suture are then crossed to form a V, with the apex just above the knot. The suture is then cut at this apex, leaving no irritating ends.

The Tantalum Gauze Inguinal Herniorrhaphy.—The tantalum gauze herniorrhaphy performed for the cure of direct inguinal hernia associated with tissue deficiency is as follows: The usual inguinal incision is made; the inguinal canal is opened by incising the fascia of the external oblique, and the structures of

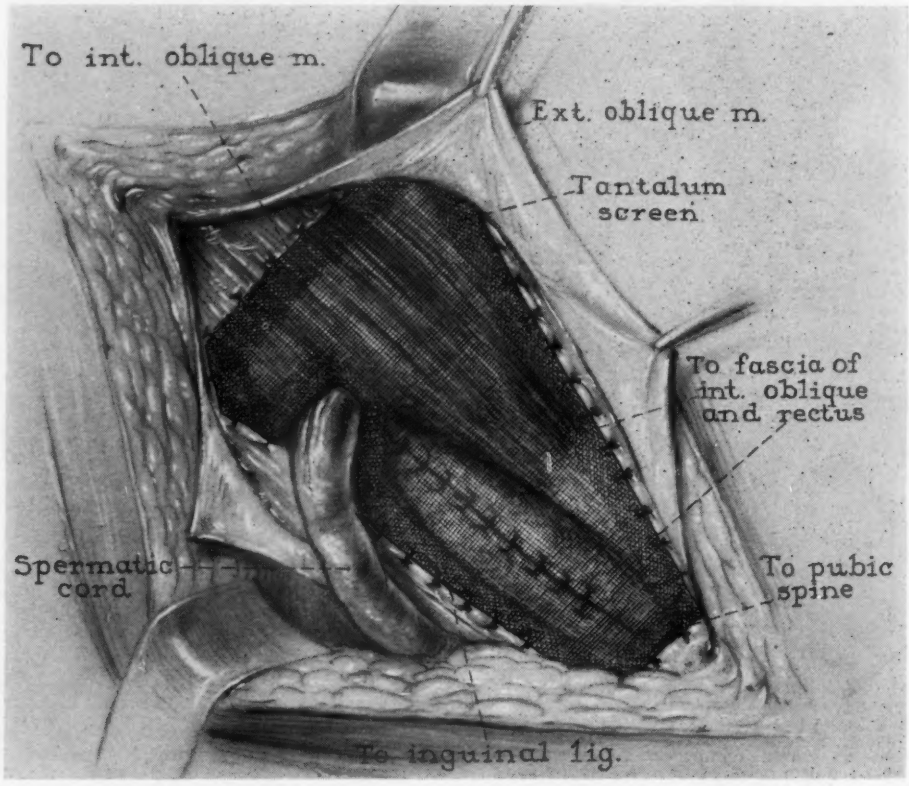

Fig. 3.—The hernial defect is covered by an implant of tantalum gauze. This is sutured medially to the periosteum of the pubis, the rectus fascia, and the fascia of the internal oblique. Laterally the implant is sutured to the shelving edge of the inguinal ligament. Superiorly, the sutures are taken in the internal oblique muscle and fascia. The spermatic cord is led through a defect in the lateral border of the implant.

the cord are isolated. These are carefully examined for an indirect sac, and retracted with a strip of Penrose rubber tubing. The direct weakness is identified and the sac treated as the situation requires, either by excision or inversion. If the rent in the transversalis fascia can be repaired, this is done (Fig. 2). No effort is made to suture a friable, attenuated, conjoined tendon to the inguinal ligament. Instead, the defect is covered with a patch of tantalum gauze. This is cut to size at the operating table, the edges doubled under, and it is sutured in place (Fig. 3). All suture material in this repair, save purse

strings and ligatures, is 10 mil tantalum wire. The usual tantalum implant is sutured medially to the periosteum of the pubic bone, the edge of the rectus sheath, and the sturdy white fascia of the internal oblique muscle. Laterally, the sutures are usually placed in the shelving edge of the inguinal ligament. On occasion, when this latter structure has been deficient, the inferior-lateral sutures have been placed in Cooper's ligament after the fashion of the McVay herniorrhaphy. The structures of the cord are brought out through a small triangular opening made high on the lateral border of the implant. The cord is then placed in the subcutaneous position by closing the fascia of the external

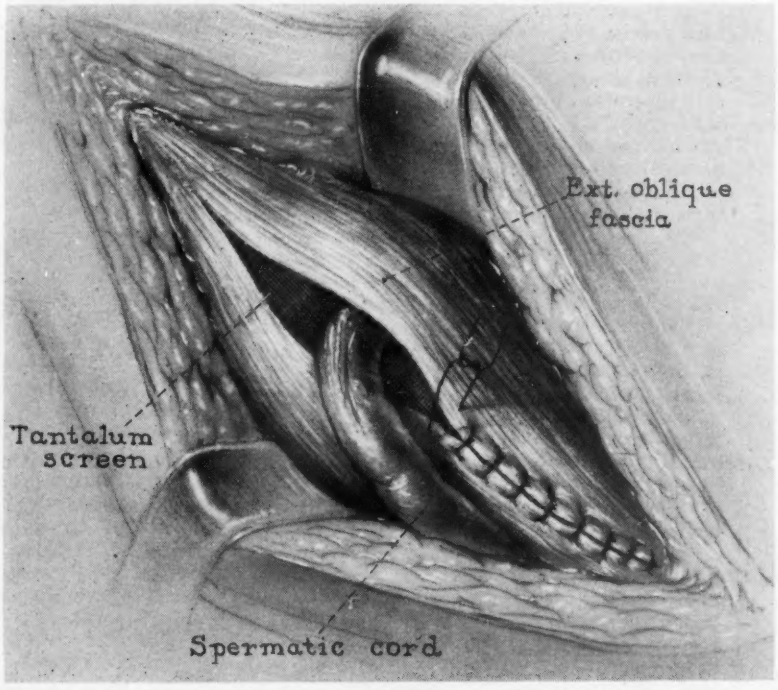

Fig. 4.—The fascia of the external oblique is sutured above the implant, placing the spermatic cord in a subcutaneous position.

oblique beneath it and over the implant (Fig. 4). The superficial fascia and skin are closed as usual. This method is equally applicable, when indicated, to indirect hernias with a large defect in the floor of the canal (as in certain sliding hernias), and to recurrent inguinal hernias. In this latter condition, since the hernia is usually direct and the inguinal region presents such a chaos, it occasionally has been necessary to use Cooper's ligament in lieu of the deficient or absent inguinal ligament. On several occasions, the lateral margin of the implant has extended from the pubic spine to the anterior-superior spine of the ilium, thus reinforcing the entire inguinal ligament.

The Tantalum Gauze Ventral Herniorrhaphy.—The problem of ventral hernia, particularly of a recurrent nature, arises periodically to perplex the surgeon. The moderate-sized ventral hernia, with good adjacent tissues, is satisfactorily repaired by one of several operative techniques. The large ventral defect, in

TABLE I

SEX AND AGE (YR.)	TYPE OF HERNIA	TYPE OF REPAIR	PERIOD OF FOLLOW-UP (MO.)	RESULT
Female, 29	Ventral—P.O. hernia through low midline incision for drainage of pelvic abscess; patient weighed 255 pounds and was 5 feet 3 in. tall	Bilateral salpingectomy and abdominal total hysterectomy, with tantalum gauze repair of large ventral hernia	26	No recurrence
Female, 63	Low midline ventral P.O. hernia; two previous repairs, the last with fascial strips and alloy steel wire; draining sinuses and skin ulceration present	Usual type of tantalum gauze implant	24	No recurrence
Male, 75	Right indirect sliding inguinal hernia, scrotal in type and incarcerated	Usual tantalum gauze repair; the trimmed edges of the sac were sutured together behind the cecum, utilizing a separate laparotomy incision	18	No recurrence
Male, 62	Huge right indirect sliding inguinal hernia, scrotal in type and incarcerated, obese and incapacitated; the inguinal defect was larger than a closed fist	Ochiectomy; tantalum gauze implant from pubic spine to anterior superior iliac spine; sac treated by laparotomy as above	10	No recurrence
Male, 34	Large bilateral direct hernias with absence of the "conjoined tendon"	Usual tantalum gauze implants; the left side was done 2 weeks after the right	6	This patient was operated 26 mo. ago; has not responded to follow-up efforts after 6 mo.
Male, 50	Right inguinal indirect and direct (saddlebag) hernia; poor fascial endowment	Usual tantalum gauze implant	25	No recurrence
Male, 68	Large right direct inguinal hernia, uncontrolled by a truss, in a patient with arrested tabes dorsalis	Usual tantalum gauze implant	19	No recurrence
Male, 75	Large left direct inguinal hernia, uncontrolled by a truss; very poor fascia	Usual tantalum gauze implant	14	No recurrence
Male, 72	Large indirect right scrotal hernia; reducible but not controlled by a truss; associated with complete destruction of the floor of the inguinal canal	Usual tantalum gauze implant	12	No recurrence; patient died of coronary heart disease 1 yr. P.O.
Male, 70	Right recurrent direct inguinal hernia; two previous herniorrhaphies; destruction lower one-third of the inguinal ligament	Tantalum gauze implant utilizing Cooper's ligament	18	No recurrence

TABLE I—CONT'D

SEX AND AGE (YR.)	TYPE OF HERNIA	TYPE OF REPAIR	PERIOD OF FOLLOW-UP (MO.)	RESULT
Male, 58	Right recurrent hernia after Halsted repair with alloy steel wire; marked tissue deficiency	Usual tantalum gauze implant	15	No recurrence
Male, 47	Left recurrent inguinal hernia; three previous repairs, the last being a Torek operation with separation of the spermatic cord and resultant hernial sacs at both inguinal rings so constructed	Excision both sacs; tantalum gauze implant utilizing Cooper's ligament and extending to the anterior-superior iliac spine	16	No recurrence
Male, 64	Bilateral recurrent direct inguinal hernias; poor fascial development and almost complete destruction of the floor of the left inguinal canal	Right Halsted herniorrhaphy with tantalum wire; left inguinal tantalum gauze implant placed in the usual manner	10	No recurrence
Male, 62	Large left direct inguinal hernia, not controlled by a truss; marked obesity and fascial inadequacy	Usual tantalum gauze implant	6	No recurrence
Male, 48	Large left recurrent inguinal hernia; three previous repairs; complete destruction of inguinal supporting structures and absence of the inguinal ligament	Tantalum gauze implant utilizing Cooper's ligament and extending to the anterior-superior iliac spine	3	No recurrence
Male, 69	Right obturator hernia with intermittent intestinal colic and a positive Howship-Romberg sign	Laparotomy; excision of sac; tantalum gauze implant over the internal obturator foramen	19	No recurrence

an obese patient whose flabby abdominal musculature is a covering rather than a support, presents a situation that demands a radical effort if a cure is to be anticipated. The use of a tantalum gauze patch over such an abdominal defect is logical and offers a simple operative procedure in lieu of a difficult one. The operation is carried out as usual to the stage of the actual repair. The peritoneum is closed and the attentuated tissues about the defect are excised back to normal structures. If it is possible to approximate the wound edges by imbrication and without tension, this is usually satisfactory and the use of tantalum mesh is not indicated. However, if imbrication cannot be accomplished without

TABLE II

WIRE DIAMETER (MIL.)	NUMBER OF BENDS (AVERAGE OF 5 DETERMINATIONS)	
	STAINLESS STEEL	TANTALUM
3	762	1,475
8	197	451
10	181	208

tension, the fascia is simply approximated over the peritoneum with interrupted sutures of tantalum wire, and a rectangular tantalum gauze implant is sutured over the repair. All sutures are taken in the fascia and without tension. In case the fascia cannot be approximated over the whole of the defect, the edges can be drawn into proximity with wire sutures and the tantalum mesh implanted directly over the peritoneum as it bulges into the hiatus. The subcutaneous tissues and skin are closed over the implant.

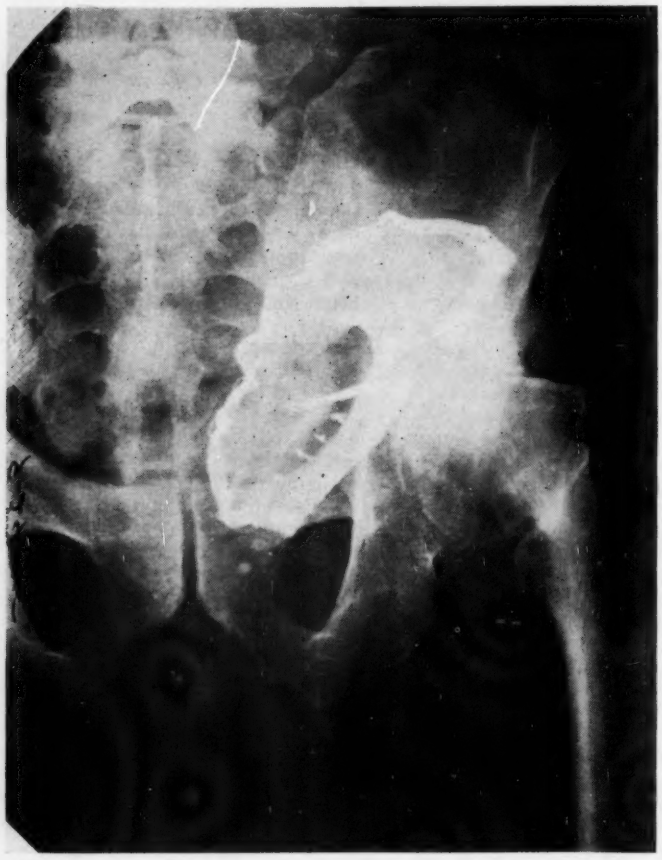

Fig. 5.—Typical x-ray view of the usual inguinal tantalum gauze herniorrhaphy.

In this connection, it is of interest to mention the tantalum gauze ventral herniorrhaphy done by Ferris[2] in October, 1945. The patient had a malfunctioning gastroenterostomy and a huge postoperative ventral hernia. This latter had occurred through an upper midline incision and extended from the xiphoid process to just below the umbilicus. The gastroenterostomy was disconnected, the opening in the jejunum closed, and partial gastrectomy with cholecystectomy was performed. The repair of the ventral hernia was then undertaken and a piece of tantalum gauze 12 by 24 cm. in size was sutured to the fascia at the edge of the defect. Underlying this tantalum screen there was nothing except the abdominal viscera, and overlying it there was only subcutaneous tissue and skin. The patient returned in May, 1946, complaining of a small ulcerated area

in the skin where it overlay a wrinkle in the tantalum gauze implant. The tantalum mesh was removed on June 3, 1946. It was dissected free from a thick layer of underlying scar tissue, which of itself was adequate to close and buttress the hernial defect, save for two small areas, 4 to 5 cm. in diameter, which were weak. These were covered by another piece of tantalum gauze of finer weave than that previously employed, and the skin incision was repaired. The result to date has been very satisfactory.

Fig. 6.—Postoperative x-ray view of a patient in whom Cooper's ligament was utilized in the repair.

The Tantalum Gauze Femoral Herniorrhaphy.—No patients have been seen with femoral hernias of such magnitude or tissue deficiency as to require a tantalum mesh implant. The inguinal approach to femoral herniorrhaphy usually is most satisfactory. If the inguinal ligament were deficient, it would be a simple matter to utilize Cooper's ligament in a tantalum gauze herniorrhaphy, as is sometimes done in certain inguinal hernias. Such an implant would completely block the internal femoral ring and should prove as satisfactory in the treatment of difficult femoral hernia as it has in the repair of inguinal hernias with associate tissue deficiency.

The Tantalum Gauze Obturator Herniorrhaphy.—One patient with obturator hernia has been treated with a tantalum gauze implant. This is the subject of a separate report. The procedure was carried out as an intraperitoneal operation. A small rectangular tantalum mesh implant was fastened over the defect

with a single suture in each corner, utilizing the periosteum in the superior sutures and the obturator membrane in the inferior ones. The obturator vessels and nerve ran beneath the lateral edge of the implant without compression.

CASE REPORTS

That a larger number of cases has not been submitted to tantalum gauze herniorrhaphy is due to the fact that, although I have been impressed by the practical utility of the operation, I believe it inadvisable to elevate the procedure to the dignity of routine treatment and employ it in all cases of hernia. The

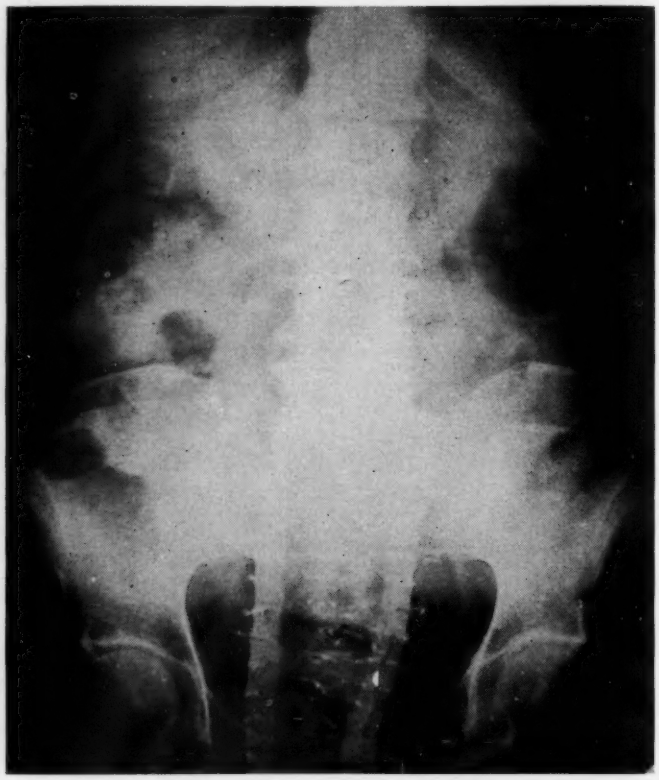

Fig. 7.—Postoperative x-ray view demonstrating the tantalum gauze implant in a ventral herniorrhaphy.

hernias so treated were of the type wherein the application of "standard operations" offered little assurance of a satisfactory result. Tissue deficiency, with or without congenital anatomic weakness, was the principal etiologic factor in every hernia in this series.

The information for this study was derived from seventeen herniorrhaphies in which tantalum gauze was implanted, with the purpose of closing and buttressing the defect present. Of these operations, two were done for postoperative ventral hernia, six were done for direct inguinal hernia, five were done for recurrent inguinal hernia, one was done for indirect hernia, two for indirect sliding hernia, and one for obturator hernia. These cases have been followed,

except one patient with a bilateral operation, at frequent intervals both by physical examination and roentgenography of the tantalum gauze implants. (Figs. 5 and 6.)

POSSIBLE COMPLICATIONS OF TANTALUM GAUZE HERNIORRHAPHY

Work-hardening.—Metal fatigue or "work-hardening" is a property of all metals and must be considered in their application to surgery. Tantalum is no exception. Repeated bending of a wire ultimately leads to fracture at the site of angulation. Tantalum is not immune to work-hardening, although it is more resistant to fatigue than many other metals commonly used for tissue implan-

Fig. 8.—X-ray finding in the same patient 17 months postoperatively. The fracture of the implant is evident, but the clinical result remains quite satisfactory after 24 months. This implant was of the 50 by 50, 5 mil tantalum gauze. It is prone to early "work-hardening" and its use has been discontinued.

tation. Tantalum wire resists work-hardening and fracture approximately twice as well as stainless steel alloy wires of comparable sizes. A few bending tests were done using 4 mm. lengths of wire held between clamps and bent through ninety degrees until fractured. The results of these tests are shown in Table II.

It is thus apparent that the larger and more rigid the wire, the more it is subject to metal fatigue. Although there have been no hernial recurrences as yet following the tantalum gauze herniorrhaphies in this series, there is x-ray evidence that some of the implanted mesh has fractured (Figs. 7 and 8). This

has become apparent after about twelve months in some patients. The 100 by 100 mesh gauze and the gauze woven of 5 mil wire is more prone to fatigue and fracture than the 50 by 50 mesh gauze woven of 3 mil wire. This was the source of considerable apprehension to me until I persuaded one of the patients to allow the exploration of a previously performed tantalum gauze herniorrhaphy at the time of operation for hernia on the other side. A small secondary incision through the old scar revealed a firm inguinal region. It was impossible to dissect the fascia of the external oblique from the underlying tantalum gauze implant, so firmly were the two united in dense white fibrous tissue. When the upper margin of the implant was freed, a finger could be slipped beneath the entire piece of tantalum mesh with ease. Although the implant was completely ensheathed in dense collagenous tissue, there were no adhesions to the underlying structures. It appeared as if a supplementary sturdy fibrous tissue sheet had been added to this region without the incorporation of underlying contiguous structures. A small corner of this implant was removed for study. The wire gauze was found embedded in dense fibrous tissue, extending approximately 3 to 4 mm. on either side of the mesh. The individual wires of the gauze were clothed by this fibrous sheath much as the steel rods in reinforced concrete. It appeared impossible for the implant, or any fragment thereof, to become fugitive in the tissues. The entire inguinal region was buttressed by a sheath of dense fibrous tissue, reinforced by a fine wire screen. There was no involvement of underlying tissues by this reaction which, microscopically, was the encapsulating reaction seen in response to the presence of a biologically inert foreign body. The work of Ferris[2] would seem to confirm these findings. With these examples in mind, it seems unlikely that a hernia could recur through an abdominal wall so reinforced. Furthermore, the factor of work-hardening would seem to assume more academic than practical importance.

The Strength of the Initial Tantalum Gauze Implant.—The ultimate strength of the tantalum gauze herniorrhaphy is dependent upon the production of a fibrous tissue patch, secondarily reinforced by the ensheathed mesh implant. However, it seems reasonable that the formation of this sheath must require several months. The question then arises as to the strength of this implant during the period of healing. Pull tests, using a Tinius Olsen testing machine, were done on ½ inch strips of 50 by 50 mesh 3 mil wire tantalum gauze. Using a ⅜ inch pull speed per minute, the average stress at the breaking point was 17.5 pounds. A wire mesh of this type, even initially, would seem to have more strength on lateral pull than the tissues to which it is anchored.

Wound Healing.—In this small series of cases, there were three wound complications. One patient, on whom a tantalum gauze herniorrhaphy had been done for direct inguinal hernia, developed a simple accumulation of serous fluid in the subcutaneous tissues. This was aspirated, a pressure dressing applied, and healing progressed without further measures. Another patient had a large recurrent ventral hernia. The overlying skin was ulcerated and two sinus tracts were present from the previous operation. Tantalum mesh was implanted in the process of the repair, and penicillin used postoperatively. There was a slight amount of serous drainage from one angle of the incision for two weeks. The

third instance of wound complication followed the repair of an enormus scrotal sliding hernia. A motion picture was taken of this procedure, during which skin towels and drapes were changed several times. The patient subsequently became febrile and several ounces of pus were evacuated from the incision. Healing progressed satisfactorily and all drainage had ceased in four weeks. From these experiences it would seem that the tantalum implant has no deleterious influence on the course of minor wound complications. The remainder of the wounds healed by first intention, without induration and with less discomfort than is usually experienced in catgut or fascial transplant herniorrhaphies.

Subjective Discomfort.—No patient in whom tantalum gauze was implanted had subjective complaint referrable to the implant. In one patient, an extremely slim, elderly man, a corner of the mesh was palpable subcutaneously, but without discomfort. Another patient was operated upon for bilateral recurrent inguinal hernias. Tissue deficiency was so marked on one side that a tantalum gauze implant was used. He knew the implant was used, but remained unable to tell in which side it was inserted. These patients were subjectively unaware of the tantalum gauze, and several of them later did hard physical work.

Testicular Complications.—There were no testicular complications in this small series of tantalum gauze inguinal herniorrhaphies. In the fourteen men operated upon, orchiectomy was done once to effect the complete closure of a huge sliding hernia. In the remaining thirteen cases, the spermatic cord was led from the abdomen through a small triangular defect in the lateral or superior border of the implant and placed in the subcutaneous position. A pressure scrotal dressing was applied at the time of operation, and these dressings were replaced by a conventional scrotal support on the fourth or fifth postoperative day. There were no instances of testicular swelling or subsequent atrophy.

DISCUSSION

The surgeons of forty years ago were much more optimistic in their discussion of herniorrhaphy than their present-day descendants. The terms "radical cure" and "ideal operation" were used carelessly. Most of these surgeons and their special operations are long since forgotten. It is not the purpose of this paper to advocate a new type of herniorrhaphy. It is the purpose of this paper to relate the experiences acquired in the use of a new material as an adjunct to the repair and closure of hernial defects where tissue deficiency plays the principal role. The use of tantalum gauze is not advocated as a routine procedure in the repair of hernias. This material is but another string to the bow of the ingenious surgeon. The application of tantalum gauze and its fibrous tissue envelope as a buttress to an inguinal canal that has failed is rational and, in my experience, satisfactory. Admittedly, the implantation of large pieces of this material is an offense to one's finer surgical sensibilities; but if the results justify the means, the pricks of ingrained convictions are soon assuaged. Serious disorders frequently demand radical measures. The use of tantalum gauze in the repair of an incapacitating incarcerated scrotal hernia is less drastic than the 75 per cent subtotal gastrectomy we so blithely perform for intractable duodenal ulcer.

The series of cases reported is small, limited as it has been by the number of patients in whom this type of repair has seemed indicated. Nevertheless, certain inferences may be drawn. Tantalum gauze implants are well tolerated by the tissues. They are not the source of subjective complaint on the part of the patient. They have not interfered with healing in those cases where wound complications have existed or supervened. The factor of work-hardening has not proved to be a real deterrent in the use of this material, as judged by results in the present group of cases to date. Each patient operated upon in this series was a likely candidate for a hernial recurrence. That there have been no recurrences to date is gratifying, but does not imply the infallibility of this procedure. However, the feasibility of the method is apparent and its further application to hernias associated with tissue deficiency is indicated.

SUMMARY

Tantalum gauze, a woven mesh of fine tantalum wire, is ensheathed by a sturdy envelope of dense collagenous tissue when implanted in the abdominal wall. This sheath, together with its reinforcing implant, may be used advantageously to buttress a hernial defect when local tissue deficiency makes the usual types of autoplastic repair impractical. The implantation of this material is not difficult. In this small series of cases, there have been no wound complications nor subjective discomfort attributable to its use. Tantalum gauze work-hardens, as do other metals, but this factor seems to be of more academic than practical importance. Its routine use in herniorrhaphy is not advocated, but a further trial of this material as an adjunct in the repair of hernias in which tissue deficiency plays a dominant role would seem justified.

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PULMONARY EMBOLISM

A Correlation of Clinical and Autopsy Studies

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AN ANALYSIS of clinical and autopsy records in the Vanderbilt University Hospital has been undertaken in an effort to aid in the clarification of the problem of pulmonary embolism as a cause of death.

Particular attention has been paid to the certainty of diagnosis and the clinical course in patients who died as a result of an embolus to the pulmonary arteries. The records were carefully examined in an attempt to determine the source of the fatal embolus.

Early in the study of these cases it became apparent that a diagnosis of pulmonary embolism was made very frequently in this hospital in both fatal and nonfatal cases. Often the diagnosis was unconfirmed and the data in retrospect seemed insufficient to justify such a diagnosis.

We believe, therefore, that a careful analysis of the data in a group of patients in whom massive pulmonary embolism was noted at autopsy may be of more value than would be any attempt to organize data on a larger group in whom pulmonary embolism might or might not have occurred.

ANALYSIS OF CASES

The Frequency of Pulmonary Embolism as a Cause of Death.—The study reported here is based upon a fifteen-year period, from 1930 to 1944, inclusive. During this period 83,984 patients were admitted to the hospital (Table I) and 35,540 operations were performed. This number includes such minor procedures as skin grafts, tonsillectomies, adenoidectomies, operations upon the eye, and the drainage of soft tissue abscesses. Bronchoscopic and esophagoscopic examinations and surgical procedures performed in the emergency room or outpatient clinic are not included.

There were 4,182 deaths in the hospital during this period and 2,580 autopsies were performed. These figures do not include stillborn infants. Death was caused by pulmonary embolism in 55 of the 2,580 patients upon whom autopsies were performed. Twenty-five of these patients had been operated upon and thirty had not. The incidence of fatal pulmonary embolism in these groups is shown in Table I.

Analysis of Autopsy Cases.—A detailed analysis of the records of the fifty-five patients examined at autopsy in whom pulmonary embolism is thought to have been the primary or immediate cause of death is presented in the accompanying tables.

Table II shows data pertaining to the seasonal, age, and postoperative occurrence of fatal pulmonary embolism.

Received for publication, April 26, 1947.

TABLE I. INCIDENCE OF FATAL PULMONARY EMBOLUS IN FIFTEEN-YEAR PERIOD, 1930-1944

Number of hospital admissions		83,984
Number of deaths in hospital (excluding stillbirths)		4,182
Number of autopsies performed (63% of deaths)		2,580
Number of operations (including ear, eye, nose and throat)		35,540
Number of fatal pulmonary emboli confirmed by autopsy		55
Expected number of fatal pulmonary emboli calculated on basis of 100% autopsies		89
Number of postoperative fatal pulmonary emboli		25
Expected number of postoperative fatal pulmonary emboli calculated on basis of 100% autopsies		39
Expected occurrence of fatal pulmonary embolism for total hospital admissions	0.11%	or 1 in 943
Expected occurrence of fatal pulmonary embolism in postoperative patients	0.109%	or 1 in 911
Occurrence of fatal pulmonary embolism in all patients examined at autopsy	2.14%	or 1 in 47

One-third of the fatal pulmonary emboli occurred in patients less than 40 years old. One patient was a 1-year-old infant with chronic bacillary dysentery.

The seasonal variation was not striking in these cases, approximately an equal number occurring in winter and summer.

Twenty-five patients had been operated upon and in fourteen of these fatal pulmonary embolism occurred within ten days after operation. Seventeen patients had abdominal operations. The types of operations are listed in Table III.

Table IV shows veins in which thrombi were found at autopsy. Twenty-eight (51 per cent) presumably came from the veins of the lower extremities. In twenty-seven (49 per cent) venous thrombi were found above the level of the superficial femoral vein. These veins include the common iliac, hypogastric, uterine, vesicle, periprostatic, ovarian, renal, adrenal, inferior vena cava, and mural thrombi in the right heart which could have been the source of the fatal embolus.

The location of the fatal pulmonary emboli is shown in Table V. Some patients who were critically ill succumbed to emboli which occluded small branches of a pulmonary artery whereas in patients whose general physical condition was good, massive emboli, which occluded the pulmonary conus or the main arteries, were always found.

Many of the fatalities from pulmonary embolism occurred among patients who had diseases which were incurable or in whom the disease was severe and the patient's prognosis grave. On the other hand, pulmonary embolism also occurred in a few patients whose prognosis otherwise seemed excellent.

The patients were, therefore, divided into three groups based upon an evaluation of the severity of the illness. Brief summaries of the entire fifty-five cases are presented in Tables VI, VII, and VIII.

Group I (Table VI) is composed of those patients who were not seriously ill prior to the occurrence of pulmonary embolism.

Group 2 (Table VII) includes patients who were seriously ill and in whom the outcome was uncertain. Many were debilitated. It is believed, however, that these patients might have recovered if pulmonary embolism had not occurred.

TABLE II. OCCURRENCE OF FATAL PULMONARY EMBOLISM

Age (in years)		
0-9	1	
10-19	2	
20-29	4	
30-39	11	
Total	18	(32.7%)
40-49	8	
50-59	14	
60-69	10	
70-79	5	
Total	37	(67.3%)
Grand Total	55	
Sex		
Male	31	
Female	24	
Total	55	
Month		
Winter		
Dec.	6	
Jan.	8	
Feb.	4	
Total	18	
Spring		
March	5	
April	3	
May	5	
Total	13	
Summer		
June	7	
July	5	
Aug.	4	
Total	16	
Fall		
Sept.	4	
Oct.	1	
Nov.	3	
Total	8	
Grand Total	55	
Operation		
Yes	25	
No	30	
Total	55	
Postoperative day fatal embolus occurred		
0-4	4	
5-9	10	
10-14	2	
15-19	2	
20-24	1	
25-29	0	
30-39	1	
Over 40	1	
More than one operation	4	
Total	25	

TABLE III. TYPE OF OPERATION

17 Abdominal Operations	
Cholecystectomy	4
Exploratory laparotomy	3
Abdominal hysterectomy	3
Exploratory laparotomy Appendectomy	1
Abdominoperineal resection, rectum	1
Incarcerated inguinal hernia	1
Repair of ventral hernia	1
Suprapubic cystotomy	1
Gastrostomy for esophageal stricture Drainage of lung abscess	1
Entercolostomy for carcinoma of cecum Laparotomy for peritoneal abscess	1
8 Other Operations	
Craniotomy	2
Incision and drainage hematoma of neurofibroma sacral region	1
Iridectomy	1
Amputation of thigh	1
Extraction of cataract	1
Radical mastectomy	1
Open reduction dislocation of hip Drainage of soft tissue abscess	1
Total	25

TABLE IV. THE LOCATION OF VENOUS THROMBI FOUND AT AUTOPSY

Unknown	25
Lower extremity below profunda femoral	3
Common femoral and iliac (One extended into vena cava; no thrombi in pelvic vessels)	4
Pelvic vessels only (prostatic, vesicle, uterine, hypogastric; two with extension into common iliac)	6
Combined pelvic and femoral veins (One had ovarian vein thrombus also)	6
Inferior vena cava, ovarian, adrenal, and renal	6
Mural thrombus of right heart	3
Mural thrombus of right heart and periprostatic	1
Mural thrombus of right auricle, left adrenal, and left popliteal	1
Total	55

TABLE V. ANATOMIC LOCATION OF FATAL EMBOLUS

Right and left main pulmonary artery	14
Conus and right and left pulmonary artery	11
Right lower lobe artery	6
Pulmonary conus only	5
Multiple small, right and left	4
Right main pulmonary artery	3
Left lower lobe artery	3
Right and left lower lobe artery	2
Right main pulmonary and left smaller arteries	2
Left main pulmonary artery	1
Right upper and lower lobe arteries	1
Right upper and lower and left lower lobe arteries	1
Left main pulmonary artery and right lower lobe artery	1
Right middle and lower and left lower lobe arteries	1
Total	55

Group 3 (Table VIII) is composed of patients who could not have recovered if pulmonary embolism had not occurred. Life expectancy was short in each case.

Table IX presents a summary of data included in Tables VI, VII, and VIII.

Fourteen patients, or one-fourth of the total number, are included in Group 1. There are twenty patients in Group 2 and twenty-one in Group 3.

The highest proportion of postoperative deaths occurred among the patients in Group 1, the lowest in Group 3.

In only eleven patients was clinical evidence of phlebitis in the lower extremities noted. The tables show that two of these cases were in Group 1, four were in Group 2, and five in Group 3. A total of fifteen patients, all in Groups 2 and 3, had bilateral edema of the lower extremities due to malnutrition, cardiac insufficiency, or renal disease which might have masked evidences of venous clotting. Examination of Tables VI, VII, and VIII shows that eight of the eleven patients in whom evidences of phlebitis were noted had infarcts in the lungs at autopsy. One of these was a patient in Group 1, four were in Group 2, and three in Group 3. Furthermore, in eight of the fifteen patients who had bilateral edema, infarcts were found in the lungs at autopsy.

There were ten patients with recorded episodes suggestive of pulmonary embolism prior to the fatal accident (Table IX). In three of these patients, one in each of the three groups, clinical signs of phlebitis were present. In all of these patients pulmonary infarction was found at autopsy.

Table IX reveals that pulmonary infarcts were found in twenty-six patients at autopsy. Only four of these were in patients in Group 1, in two of whom there was clinical evidence of previous pulmonary infarction. Phlebitis was noted in only one of the four. Thirteen (65 per cent) of the patients in Group 2 exhibited pulmonary infarcts at autopsy. In three of these signs of phlebitis were present before death and in four there was clinical evidence of previous pulmonary embolism; one other patient exhibited signs of both phlebitis and pulmonary embolism prior to the fatal accident. Among the remaining five patients, four had bilateral edema thought to be due to nutritional deficiencies or cardiac decompensation.

In Group 3 pulmonary infarcts were found in nine patients (43 per cent) at autopsy. Three of these had clinical signs suggestive of pulmonary embolism and one of these patients also had bilateral thrombophlebitis. Two other patients of the nine had evidence of phlebitis. In three patients there was massive edema which was due to cardiac insufficiency in two and cystic disease of the kidney in one. It should be recalled that this group is composed of patients with far-advanced incurable diseases.

It is noteworthy that of the twenty-five patients upon whom operation was performed, evidence of pulmonary emboli prior to death was found at autopsy in only nine. Thus, sixteen died as a result of a single pulmonary embolus. Emboli which occluded smaller arteries caused death only in severely ill or debilitated patients.

TABLE VI.—GROUP 1, UNEXPECTED SUDDEN DEATH DUE TO PULMONARY EMBOLUS, PATIENT IN GOOD GENERAL CONDITION

PATIENT, RACE, SEX, AGE	CLINICAL DATA				AUTOPSY DATA		
	DIAGNOSIS	OPERATION	REMARKS	PHLEBITIS PUL. INFARCT	VEINS INVOLVED	PUL. INFARCT	EMBOLUS
W. S., W, M, 48	Duodenal ulcer, hemorrhage		Profuse hemorrhages, Hb. 7 Gm.	None	Rt. auricle and periprostatic	None	Massive rt., lt., and conus
H. L., W, M, 59	Cholecystitis	Cholecystectomy	Uncomplicated P.O. course, died 8th P.O. day, Hb. 13 Gm.	None	Unattached thrombus in inferior vena cava	None	Massive rt., lt., and conus
E. B., N, F, 31	Fibromyoma uterus	Hysterectomy	Uncomplicated P.O. course, died 11th P.O. day, Hb. 13 Gm.	No phlebitis, slight elevation of temp., pulse and resp. 8th P.O. day	Rt. uterine into int. iliac, also lt. ovarian	None	Massive rt., lt., and conus
C. A., W, M, 37	Acute cholecystitis	Cholecystectomy	Uncomplicated P.O. course, died 7th P.O. day, Hb. 14 Gm.	None	Unknown	Recent	Massive rt., lt., and conus
S. S., W, M, 30	Rt. hydronephrosis, perinephric abscess	Exploratory laparotomy, appendectomy	Fever 100-104° F., died 15th P.O. day, Hb. 14 Gm.	None	Lt. renal into inf. vena cava loosely attached	Infarcts present	Massive conus
E. R., W, F, 55	Chronic cholecystitis, diabetes mellitus	Cholecystectomy	Temp. 100-100.6° F. P.O., died 5th P.O. day, Hb. 13 Gm.	Thrombosed (old) varicose veins of lt. calf	Unknown	None	Massive conus
M. C., W, F, 56	Intertrochanteric fracture, lt. femur		Temp. 100-100.8° F., Hb. 13 Gm.	None	Mural thrombus in rt. auricle	None	Massive rt. and lt.

M. L., W, F, 42	Varicose veins and ulcers, cholecystitis, chronic	Skin grafts, cholecystectomy	Temp. to 101° F., died 17th P.O. day, Hb. 11 gm.	None	Unknown	None	Massive rt., lt., and conus
T. L., W, M, 62	Cellulitis of face, benign prostatic hypertrophy	Suprapubic cystostomy	Uncomplicated P.O. course except phlebitis, died 6th P.O. day, Hb. 13 Gm.	Thrombophlebitis lt. calf, first noted 10 min. before death	Lt. pudendal and int. iliac into common iliac, femoral not involved	None	Massive rt. and lt.
J. E., W, M, 64	Cataract, bilateral	Extraction cataract rt. eye	Spontaneous pneumothorax 7th P.O. day, died 14th P.O. day, Hb. 15 Gm.	None	Int. and ext. iliac into common iliac and vena cava, loosely attached	None	Rt. pul. artery
V. S., N, F, 44	Fibromyoma of uterus, tubo-ovarian abscess, rt.	Hysterectomy	Uncomplicated P.O. course, died 9th P.O. day, Hb. 9.5 Gm.	None	Rt. hypogastric	None	Rt. main pul. artery and lt. smaller artery
E. S., W, F, 65	Carcinoma of breast, acute mastitis, biliary calculi	Radical mastectomy	Uncomplicated P.O. course, died 5th P.O. day, Hb. 13.5 Gm.	None	Unknown	None	Massive rt., lt., and conus
A. H., W, M, 48	Chronic sinusitis, pul. infarction, multiple		Temp. 99-102° F., Hb. 13 Gm.	No phlebitis, signs of pul. infarct	Unknown	Yes, multiple	Massive rt. and lt.
N. H., W, M, 17	Furunculosis, thrombophlebitis, popliteal and jugular		Lymphangitis, rt. leg, furunculosis of lower extremities, multiple emboli, R.B.C. 4.8 mil., died day of admission	Rt. popliteal, lt. external jugular; signs of pul infarct	Fixed thrombus in rt. int. iliac, unattached in ext. and common iliac, neck veins not examined	Yes, multiple	Massive rt. and lt.

TABLE VII, GROUP 2, SEVERE ILLNESS BUT RECOVERY LIKELY WITHOUT EMBOLUS

PATIENT, RACE, SEX, AGE	DIAGNOSIS	CLINICAL DATA			AUTOPSY DATA		
		OPERATION	REMARKS	PHLEBITIS PUL. INFARCT	VEINS INVOLVED	PUL. INFARCT	EMBOLUS
W. G., W, M, 20	Convulsions, post-traumatic	Craniotomy	Stormy P.O. course, temp. 101-105° F., died 8th P.O. day, Hb. 10 Gm., transfusions	No phlebitis, signs of pul. infarct	Periprostatic	Yes, rt. lung	Massive rt., lt., and conus
C. T., W, F, 36	Puerperal sepsis, septicemia, hemolytic str.		Septic course, positive blood culture, also aspiration vomitus, Hb. 6-10 Gm., 11 transfusions	No phlebitis, signs of pul. infarct	Rt. ovarian, lt. renal and adrenal inf. vena cava organizing thrombus fixed to vein wall	Yes, septic staph. aureus	Lt. lower lobe artery
W. W., N, M, 63	Diabetes mellitus, general arteriosclerosis, gangrene of lt. foot	Amputation lt. mid-thigh (emergency)	Died 2nd P.O. day, N.P.N. 120, sec. anemia, Hb. 11 Gm.	None	Lt. superficial femoral (amputation stump)	No	Massive rt. and lt.
B. M., W, F, 52	Esoph. varicosities with hemorrhage, cirrhosis of liver		Repeated massive hemorrhage, Hb. 4-6 Gm., ascites, pneumonia, multiple transfusions	Lt. femoral, no signs pul. infarction	Lt. int. and ext. iliac into common iliac, unattached thrombi in inf. vena cava	Yes, multiple	Rt. and lt. multiple smaller vessels
W. S., W, M, 49	Infected polypi of rectum and colon, anemia, secondary, wound disruption	Exp. laparotomy, secondary wound closure	Fever 100-101° F., diarrhea for weeks, increasing weakness, Hb. 6-8 Gm., malnutrition	None, bilateral edema of feet and legs	Lt. external iliac, femoral and popliteal, loosely, attached	Yes, multiple	Multiple small vessels
P. B., N, M, 31	Stricture of esophagus, abscess of rt. lung	Gastrostomy, drainage of lung abscess	4 operations, last 4 days before death, Hb. 8 Gm.	None	Unknown	Yes	Rt. main pul. artery
J. S., W, M, 24	Gliosis lt. frontal, post-traumatic, decubiti, buttocks	Craniotomy, excision of motor cortex	Stormy P.O. course, temp. 102-105° F., died 15th P.O. day, Hb. 9-10 Gm.	Edema of lt. leg and thigh	Lt. common iliac, ext. and int. iliac vesicle, prostatic, gluteal and rt. hypogastric, loosely attached	Yes	Massive rt. and lt.

W. D., W, M, 72	Sliding inguinal hernia, strangulated, bronchopneumonia, bilat., paroxysmal auricular fibrillation	Emergency herniorrhaphy	Stormy P.O. course, temp. 102-105° F., died 6th P.O. day, Hb. 12 Gm.	None	Rt. auricle	No	Massive rt., lt., and conus
R. G., W, M, 53	Ventral hernia, coronary thrombosis, recent (autopsy)	Repair of hernia	Bronchopneumonia, bilat., improving at death on 23rd P.O. day, Hb. 14 Gm.	No phlebitis, signs of pul. infarct	Unknown	Yes	Massive rt. and lt.
M. D., W, M, 48	Glomerulonephritis (nephrotic stage), passive congestion of abdominal viscera		General anasarca, N.P.N. 80, T.S.P. 4.2, slow downhill course, Hb. 10 Gm.	Bilateral edema	Unknown	No	Massive rt. and lt.
C. S., W, F, 36	Chronic ulcerative enterocolitis		Temp. 100-101° F. for 3 weeks; diarrhea, malnutrition, increasing weakness, Hb. 11.5 Gm.	Slight edema of both legs	Unknown	No	Lt. lower lobe
D. A., W, M 34	Typhoid fever		Temp. 103-105° F. for 3½ weeks, abdominal distention, malnutrition, Hb. 10 Gm., positive blood culture	Thrombophlebitis of lt. lower extremity, signs of pul. infarct	Lt. femoral common iliac and hypogastric and int. saphenous unattached in common iliac	Yes, septic	Lt. lower lobe
C. B., W, F, 55	Fibromyoma of uterus, pelvic peritonitis, perforation of cecum, operative	Abdominal hysterectomy	Temp. 104° F., P.O. subsiding to normal in six days, abdominal distention, died 8th P.O. day, Hb. 9 Gm.	None	Unknown	No	Massive rt. and lt.
L. Q., W, F, 39	Cardiac decompensation, 3 mo. post partum		Malnourished, marked edema all extremities, died 3rd hosp. day, Hb. 7 Gm., T.S.P. 5.3	Massive edema	Ovarian, uterine veins, bilateral	Yes, multiple	Rt. main multiple small
M. W., W, F, 29	Tube, ovarian abscess, ruptured; genal peritonitis, incomplete abortion		Temp. 100-101° F., rigid abdomen, Hb. 4.6 Gm.; given 4 transfusions but course progressively down hill, died 10th hosp. day	Bilateral edema	Lt. ovarian and both renal veins	Yes, bilateral multiple	Lt. main rt. lower lobe

TABLE VII—CONT'D

PATIENT, RACE, SEX, AGE	DIAGNOSIS	CLINICAL DATA: OPERATION	CLINICAL DATA: REMARKS	CLINICAL DATA: PHLEBITIS PUL. INFARCT	AUTOPSY DATA: VEINS INVOLVED	AUTOPSY DATA: PUL. INFARCT	AUTOPSY DATA: EMBOLUS
W. H., W, M, 1	Chronic bacillary dysentery, marasmus, sec. anemia		Marked malnutrition, temp. 103° F. for several weeks, normal 1 mo. before death, Hb. 10 Gm.	None	Unknown	No	Massive conus
C. H., W, F, 79	Fracture of neck of femur, old left hemiplegia (abscess of epicardium found at autopsy)		Temp. 102-104° F. 9 days before death, Hb. 10 Gm.	Bilateral edema	Unknown	Yes	Lt. main artery, infarct. lt. lower lobe
M. A., W, M, 14	Staph. bacteremia and empyema, staph. pericarditis		Temp. 102-105° F. daily, also multiple lung abscesses, abscess kidney, subgluteal and thyroid gland, Hb. 15 Gm.	No phlebitis, signs of pul. infarct	Unknown	Yes, septic	Massive rt. heart and conus
H. H., W, M, 57	Tuberculous pericarditis, arteriosclerotic heart disease		Decubitus ulcers and cellulitis, temp. 101-102° F. daily, Hb. 12 Gm.	Bilateral edema	Unknown	No	Rt. lower lobe
S. H., N, F, 54	Carcinoma of rectum, acute P.O. intestinal obstruction	Abdominoperineal resection of rectum, laparotomy for intestinal obstruction	Intestinal obstruction following resection, died 8th day after resection, Hb. 10 Gm.	Edema of rt. lower extremity	Rt. and lt. hypogastric into rt. ext. iliac	Yes	Massive rt. and lt.

TABLE VIII, GROUP 3, PATIENTS WITH FAR-ADVANCED DISEASE AND SHORT LIFE EXPECTANCY REGARDLESS OF EMBOLUS

		CLINICAL DATA			AUTOPSY DATA		
PATIENT, RACE, SEX, AGE	DIAGNOSIS	OPERATION	REMARKS	PHLEBITIS PUL. INFARCT	VEINS INVOLVED	PUL. INFARCT	EMBOLUS
H. H., W, M, 41	Neurofibroma (massive) of sacrum, hematoma massive infection and sec. hemorrhage	Incision and drainage of hematoma	Cl. welchii infection of back, temp. 102° F. daily, frequent hemorrhages, expired 30th P.O. day	None	Unknown	None	Rt. main pul. artery
D. A., W, M, 65	Fibrosarcoma, abdominal, extensive; lung abscess		Died few hours after admission, suddenly	Lt. leg	Attached thrombus, rt. common iliac extending into femoral and vena cava	None	Rt. and lt. secondary pulmonary arteries
J. B., W, F, 57	Multiple fractures of ribs; metastatic carcinoma of lungs, ribs, axilla from breast; injury of eye	Iridectomy for eye injury	Temp. 99-102° F. daily, marked malnutrition	None	Lt. popliteal not attached	None	Massive conus, rt. and lt. pulmonary arteries
A. W., W, M, 47	Tetanus, general paresis		Convulsions, coma, temp 99-104° F. daily, died 6 days after admission	None	Prostaticovesicle plexus	None	Massive rt. and lt.
T. M., W, F, 31	Carcinoma of cecum with necrosis of bowel; metastases to mesenteric and aortic nodes	Enterocolostomy; laparotomy for peritonitis	Temp. 100-102° F., progressive downhill course	Edema of rt. lower extremity	Rt. common iliac	Yes, recent	Rt. lower lobe
H. W., N, M, 55	Carcinoma of stomach with metastases to liver and pleura		Arteriosclerotic heart disease, benign prostatic obstruction, marked malnutrition	None	Unknown	None	Massive conus, rt. and lt. pul. arteries

TABLE VIII.—CONT'D

PATIENT, RACE, SEX, AGE	DIAGNOSIS	CLINICAL DATA			AUTOPSY DATA		
		OPERATION	REMARKS	PHLEBITIS PUL. INFARCT	VEINS INVOLVED	PUL. INFARCT	EMBOLUS
J. D., W, M, 61	Carcinoma of gall bladder; metastases to liver, pancreas, and duodenum	Exploratory laparatomy	Temp. 99-100° F., died 14 hr. after operation	None	Periprostatic	None	Massive conus
H. T., W, F, 25	Arteriosclerotic heart disease; cardiac decompensation		Cardiac insufficiency despite digitalization, increasing fever to 105° F.	Rt. leg	Lt. adrenal, lt. popliteal; mural thrombus rt. auricle	Yes, recent	Rt. and lt. lower lobe arteries
I. E., W, F, 55	Hypertensive cardiovascular disease, cardiac decompensation		Cardiac insufficiency despite digitalization, temp. 100-103° F. daily	Bilateral edema of lower extremities	Unknown	Yes	Rt. lower lobe, lt. lower lobe
J. M., W, M, 71	Rheumatic heart disease, cardiac decompensation		Cardiac insufficiency despite digitalization, temp. 101° F.	Bilateral edema	Mural thrombus in rt. auricle	None	Massive rt. and lt.
N. H., W, M, 65	Pyelonephritis, hypertensive cardiovascular disease, cardiac decompensation, ulcer of lt. foot		Temp. 98-106° F., cardiac insufficiency despite digitalization	Edema of lt. leg	Unknown	None	Rt. upper and rt. lower lobes
P. P., W, M, 70	Arteriosclerotic heart disease with failure		Cardiac insufficiency despite digitalization	Brawny edema of both feet and legs	Unknown	Yes, recent	Rt. lower lobe
J. C., W, M, 72	Fracture of neck of femur, hypertensive heart disease with failure		Cardiac insufficiency despite digitalization, temp. increasing to 105° F., increasing stupor to coma	Edema of both lower extremities, signs of pul. infarct	Unknown	Yes	Rt. lower lobe

R. E., W, M, 63	Arteriosclerotic heart disease with failure, bronchopneumonia bilateral		Cardiac insufficiency despite digitalization, temp. 102-104° F. for two weeks, gradual decline	Generalized edema	Unknown	None	Rt. lower lobe
J. D., W, M, 53	Arteriosclerotic heart disease with failure		Cardiac insufficiency despite digitalization, temp. 101-102° F. daily	Edema of all extremities	Unknown	None	Rt. middle and lower and lt. lower lobe arteries
A. G., W, F, 62	Arteriosclerotic heart disease with failure, acute cholecystitis, toxic nodular goiter	Anesthesia (general) only, operation abandoned because of poor condition	Cardiac insufficiency despite digitalization, temp. 101° F., died 11th P.O. day	Edema of both lower extremities, signs of pul. infarcts	Unknown	Multiple	Massive rt. and lt.
C. J., W, M, 30	Fracture of pelvis, rupture of bladder and urethra, dislocated hip	Open reduction of disloc. hip; drainage of abscess	Peri-urethral abscess, septicemia, bronchopneumonia, bilateral; temp. 101-104° F. daily, died 16th P.O. day	None	Unknown	None	Rt. lower lobe
S. E., W, F, 57	Papillary carcinoma of bladder, vegetative endocarditis, rt. hemiplegia		Cerebral accident, temp. 100-103° F. daily, patient comatose after cerebral accident	None	Rt. femoral and ext. iliac with puriform softening	Multiple small	Multiple rt. and lt. small secondary vessels
A. D., W, F, 38	Congenital cystic kidney, bilateral; pyelonephritis, perforation of gastric ulcer with abscess of lt. upper abdomen		Temp. 101-102° F., gradual downhill course, coma, death	Edema of both lower extremities	Renal, bilateral into inferior vena cava	Yes, recent	Rt. upper and lt. lower
J. G., W, F, 62	Abdominal carcinomatosis generalized	Exploratory laparotomy	Temp. 101-102° F. for two weeks, gradual downhill course, died 2nd P.O. day	None	Unknown	None	Massive rt. and lt.
A. J., W, F, 42	Adenocarcinoma of pancreas (head) and liver		Temp. 101-102° F. for six weeks	Thrombophlebitis of rt. and lt. legs, signs of pul. infarct	Rt. ovarian into inf. vena cava	Multiple	Massive rt. and lt.

TABLE IX

	GROUP 1	GROUP 2	GROUP 3	TOTAL
Number of cases in each group	14	20	21	55
Average age	47	40	53	
Postoperative	10 (71%)	9 (45%)	6 (28%)	25
Clinical evidence of phlebitis (lower extremities	2 (14%)	4 (20%)	5 (24%)	11
Edema bilateral (lower extremities)	0	7 (35%)	8 (38%)	15
Clinical signs suggesting pulmonary infarction prior to fatal accident	2 (14%)	5 (25%)	3 (14%)	10
Pulmonary infarction prior to fatal embolus (found at autopsy)	4 (28%)	13 (65%)	9 (43%)	26
Location of thrombus found at autopsy				
Unknown or below profunda femoris	6 (43%)	10 (50%)	12 (58%)	28
Above profunda and below bifurcation of vena cava (including pelvic vessels)	5 (36%)	6 (30%)	5 (24%)	16
Above bifurcation of vena cava	3 (21%)	4 (20%)	4 (18%)	11
Location of fatal embolus in pulmonary vessels				
Massive bilateral embolus	12 (86%)	10 (50%)	8 (38%)	30
Main artery on one side	2 (14%)	4 (20%)	1 (5%)	7
Smaller emboli	0	6 (30%)	12 (58%)	18

Table IX shows that all of the patients in Group 1 (fourteen) died of massive emboli to large pulmonary arteries while twelve patients (58 per cent) in Group 3 died of emboli to small pulmonary arteries.

Origin of Embolus.—The autopsy records were studied in an attempt to determine the source of the embolus. The veins in which thrombi were demonstrated are listed in Table IV. A summary of these findings is included in Table IX. The veins were carefully examined at autopsy down to the thigh. In some cases the popliteal and superficial femoral veins were examined but this was not done routinely. The calf and plantar vessels were not examined.

There were twenty-five cases in which no thrombus was found. In three cases thrombi were demonstrated in the popliteal or the superficial femoral veins. If we assume that all pulmonary emboli in which the source was not found came from the lower extremities, a total of twenty-eight (51 per cent) of the fatal pulmonary emboli originated in the veins of the lower extremities below the opening of the profunda femoris.

There were four cases in which thrombi were found in the common femoral or common iliac veins and were not demonstrated elsewhere. In one of these cases the thrombus was fixed to the walls of the iliac vessel and appeared to have originated there. The other three may have originated in vessels lower in the leg or thigh and extended to the femoral or iliac.

Thrombosis of the pelvic veins or a combination of the pelvic and femoral veins was demonstrated in twelve patients. These pelvic vessels included the uterine, prostatic, vesicle, pudendal, and hypogastric veins. There were eleven cases in which venous thrombosis was found in vessels above the bifurcation of the vena cava. These include the ovarian, renal, adrenal, and mural thrombi in the right auricle. Many of these thrombi extended into the inferior vena cava.

Thus, in twenty-seven (49 per cent) of the fifty-five patients, the fatal pulmonary emboli could have originated from thrombi in veins superior to the level of the profunda femoris vein. Since there were twenty-eight patients in whom no thrombus was found above the level of the profunda femoris vein it was assumed that the fatal pulmonary embolus originated from the veins of the lower extremities. It seems important, therefore, to determine whether there were indications in these cases for ligation of the superficial femoral vein. Twelve of the twenty-eight patients had far-advanced disease and short life expectancy even if pulmonary embolus had not occurred. Venous ligation in those patients would have been difficult to justify even in the presence of signs of venous thrombosis. In only four of the remaining sixteen patients were there any signs to indicate venous thrombosis.

There were six patients in Groups 1 and 2 not included among the sixteen discussed previously who gave evidence of venous thrombosis prior to the fatal embolis. All of these had thrombi, demonstrated at autopsy, in veins above the profunda femoris and would, therefore, probably not have benefited by ligation of the superficial femoral vein.

CONCLUSIONS

Fatal pulmonary embolism occurs at all ages but is more frequent in the advanced groups. Of more importance is the fact that its occurrence increases with the degree of severity of illness of the patient.

Trauma did not appear to have a significant influence upon the frequency of occurrence of pulmonary embolism in this group of patients.

Homans,[1] Rössle,[2] Hunter, Sneeden, Robertson, and Snyder,[3] and others, have demonstrated that clots are frequently found, at autopsy, in the small veins of the legs. We believe it to be of importance to emphasize the fact that in twenty-three of the fifty-five autopsy records reviewed in this study, thrombi were found in veins of the pelvis or the upper abdomen. These vessels include the renal and adrenal veins, the ovarian and spermatic veins, and, in three cases, thrombi in the right side of the heart. If the fatal embolus originated in these pelvic and abdominal veins, a few of the patients might have been saved by ligation of the inferior vena cava.

Clinical evidence of phlebitis was found in only eleven patients among the fifty-five who died of pulmonary embolism, and in five of these patients life expectancy was short because of incurable disease. In all of the remaining six patients thrombi were found at autopsy in the internal iliac vein or its branches. Ligation of the femoral veins could not have prevented pulmonary embolism if the embolus originated in the pelvic veins but ligation of the inferior vena cava might have done so. Furthermore, the presence of swelling or tenderness in the lower extremities does not exclude the presence of additional thrombi in other veins.

The restriction of activity or the fixation of patients in bed is probably of importance in causing thrombosis in veins. During the fifteen-year period from 1930 to 1944 inclusive there were 2,107 admissions to the Vanderbilt Uni-

versity Hospital for pulmonary tuberculosis. Most of these patients were confined to bed before admission and all were kept in bed during hospitalization. These patients, with rare exceptions, were permitted to move about in bed without restriction. Very few were critically ill during the period of hospitalization. Fatal pulmonary embolism did not occur in any of these patients. The importance of the absence of fixation and of prolonged muscular relaxation should be stressed instead of ambulation as a means of preventing venous stasis.

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TATTOOING WITH MERCURY SULFIDE FOR INTRACTABLE ANAL PRURITUS

With Brief Reference to Vulval Pruritus and Evaluation of Results

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IN THIS article there is presented an analysis of 93 of a total of 106 patients suffering from intractable anal pruritus who had been treated by tattooing with mercury sulfide[1] during the period between October, 1938, and November, 1942, and who had been followed personally and adequately for from six months to four years.* At some time prior to tattooing, all of these patients had received various forms of treatment without lasting benefit. The antecedent therapeutic procedures included topical medicines, endocrine drugs, irradiation, psychotherapy, subcutaneous injection of oil-soluble, long-acting "anesthetic solutions" or alcohol, anorectal operative procedures, or combinations of these forms of therapy (Table I).

MATERIAL AND RESULTS

The pertinent data concerning this group of patients are depicted in the accompanying tables. Table II shows that fifty-three patients of this series had had regional itching for ten years or longer. Table III shows that these patients had had moderate to severe degrees of characteristic local cutaneous changes which are encountered in advanced chronic anal pruritus.[2] Their circumanal skin was discolored grayish-white, moist, superficially fissured or otherwise ulcerated, indurated, thickened, and folded; in a few patients the skin was reddish, smooth, and glistening. In forty of these unselected cases the histologic studies showed various degrees of edema and inflammatory reaction in the upper portion of the skin. Occasional erosion and excoriation were also observed. It is realized that previous therapy, especially irradiation, influenced the gross and microscopic cutaneous appearance. Leucoplakic perianal and anal lesions resembling those seen in moderately advanced kraurosis vulvae were observed in seven patients.

All of these fifty-three patients, as illustrated in Table IV, were, in varying degrees, relieved of the troublesome itching. Thirty-eight patients graded their therapeutic response as good, while fifteen graded theirs as satisfactory. The itching usually ceased immediately after tattooing and the texture of the skin returned to normal or near normal in three to four weeks.

Ten of the thirty-eight patients who regarded their therapeutic results as good had had anal pruritus for over twenty-five years and had the most advanced cutaneous changes I have ever seen. Significantly, their therapeutic

Presented in part, with cinematographic illustration, at a meeting of the Philadelphia Proctologic Society, Dec. 18, 1946.

Received for publication, Jan. 31, 1947.

*This study was completed in October, 1942, just prior to my entry into the Army, but its publication was postponed for obvious reasons.

TABLE I. IMPORTANT THERAPY EMPLOYED PRIOR TO TATTOOING*

THERAPY	NUMBER OF PATIENTS
Topical medication (ointments and lotions)	All
Irradiation	65
Subcutaneous injection of oil-soluble "anesthetics"	85
Subcutaneous injection of alcohol	8
Anorectal operations (hospital or office procedures)	42
Endocrine	14
Psychotherapy	9
Various combinations of the foregoing procedures	All

*This information was obtained from the patients and not always from their physicians or hospitals.

TABLE II. DURATION OF PRURITUS

GROUP	YEARS	NUMBER OF CASES
I	15 or longer	24
II	10 or longer	29
III	5 or longer	33
IV	1 or longer	7
	Total number of cases	93

response was the most gratifying. Although advanced in years, these patients underwent a drastic change in disposition; by their statement and definition, they attained "a new lease on life."

The fifteen of the fifty-three patients in whom "satisfactory" results were obtained have occasionally experienced short-lived episodes of mild pruritus for which further treatment is neither indicated nor desired as they are satisfied with the therapeutic outcome. Some of these patients had a light cutaneous deposit of mercury sulfide as well as external and internal hemorrhoids, associated with recurrent stasis and congestion. For experimental reasons, these hemorrhoids were deliberately left undisturbed. It should be pointed out that external hemorrhoids, tabs, or redundant perianal skin are technically difficult to tattoo properly.

Interestingly, Tables III and IV also show that in sixteen patients of Group III who had had pruritus for five years or longer, but who had also exhibited moderate to advanced cutaneous local manifestations, good therapeutic results had also been obtained.

TABLE III. GROSS CUTANEOUS MANIFESTATIONS CONSISTENT WITH PRURITUS

GROUP	PRESENT (MODERATE TO SEVERE) NUMBER OF CASES	ABSENT OR MINIMAL NUMBER OF CASES
I	24	0
II	29	0
III	16	17
IV	1	6

TABLE IV. RESULTS OF TATTOOING WITH MERCURY SULFIDE

GROUP	GOOD (NUMBER OF CASES)	SATISFACTORY (NUMBER OF CASES)	POOR (NUMBER OF CASES)
I	20	4	0
II	18	11	0
III	16	4	13
IV	1	2	4

Of the twenty-three patients who exhibited either minimal or no cutaneous changes, only six responded satisfactorily to tattooing with mercury sulfide, while the remaining seventeen patients failed to improve.

COMMENT

From the foregoing analysis and study, it is apparent that tattooing with mercury sulfide is effective for chronic recalcitrant anal pruritus that is associated with characteristic cutaneous changes. Confirmation of these results has indirectly been elicited in an experimental study of a small series of cases of intractable vulval pruritus. Those patients who manifested cutaneous changes, especially the hypertrophic manifestations, have responded well to tattooing with mercury sulfide.[3] In four of these women contemplated radical vulvectomy became unnecessary following tattooing. In contrast, fifteen women with vulval pruritus who showed no cutaneous changes have uniformly failed to respond to tattooing with mercury sulfide.*

Most of the patients who had not exhibited characteristic cutaneous manifestations, except for scratch marks, were highly nervous and frustrated individuals. Four of them had received prolonged psychotherapy by recognized experts prior to tattooing without apparent benefit. The psychic factors of these individuals were extremely difficult to evaluate as one could not always be sure of what was cause or what was effect. In some of these individuals the mental status was not apparent before tattooing, while others I treated for experimental reasons because I realized that the continuance of anal itching was conducive to a variety of psychotic manifestations in these neurotic patients. This policy was motivated in 1939 by the satisfactory results obtained in some "psychoneurotic" patients.[4]

The satisfactory results obtained in the six patients of Groups III and IV who had had either minimal or no cutaneous perianal skin changes may to a degree be ascribed to psychotherapeutic influences. This interpretation was recognized in the early course of my studies[4] as I then stated, "It is realized that in some instances tattooing with mercury sulfide, like other therapeutic procedures, may in addition to the pharmacodynamic action exert a psychotherapeutic effect although in normal (nonneurotic) patients our control studies of tattooing with mercury sulfide indicated that the psychic effect is of no therapeutic value in relieving pruritus."

Although individuals with anal pruritus who have minimal or no cutaneous changes are poor candidates for tattooing with mercury sulfide, these patients may nevertheless be given a trial of tattoing only before other drastic therapeutic procedures, such as the subcutaneous injection of ethyl alcohol[5] or the radical resection of the anoperianal skin,[6] are contemplated.

ANOGENITAL PRURITUS

In two men with severe concomitant anal and scrotal pruritus, some amelioration of scrotal itching occurred after the cessation of anal pruritus follow-

*Most of the gynecologic aspects of this study were conducted with the cooperation of the late Dr. S. H. Geist, Mount Sinai Hospital, New York, N. Y.

ing tattooing with mercury sulfide. Subsequent tattooing of the scrotal skin was ineffective in completely eliminating the itching of the scrotum.

To date I have successfully treated twelve women with pruritus ani and pruritus vulvae by tattooing of the anal and perianal regions only. In five of these patients tattooing of the vulva had also been contemplated, and the anoperineal region was tattooed as a preliminary procedure. Following this maneuver there occurred sufficient subjective and objective improvement of the vulval itching so that further treatment became unnecessary.

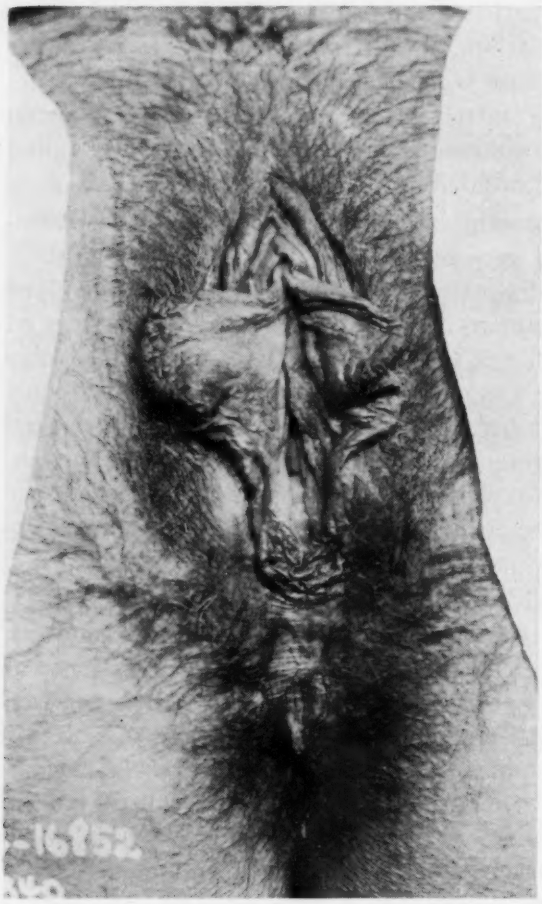

Fig. 1.

Fig. 2.

Fig. 1.—Pretattoo appearance of anogenital pruritus (see Figs. F and G).
Fig. 2.—Pretattoo appearance of "hypertrophic" vulvitis with areas of leucoplakia (see Fig. H).

GENERAL PROCEDURE

The following procedures are now carried out prior to tattooing with mercury sulfide: (1) A general survey including a patch test for sensitivity to mercury using 2 per cent ammoniated mercury ointment; positive reactors should never be tattooed with mercury or its derivatives. (2) The eradication of anorectal or colonic lesions as well as excision of redundant perianal skin.

(3) The administration of estrogenic therapy to women who develop anal pruritus at or after menopause. Usually about 150,000 to 250,000 R.U. of estradiol benzoate* are administered in biweekly intramuscular doses of from 6,000 to 10,000 R.U. If the localized pruritus is unrelieved by hormonal therapy, tattooing is carried out.

Fig. 3.

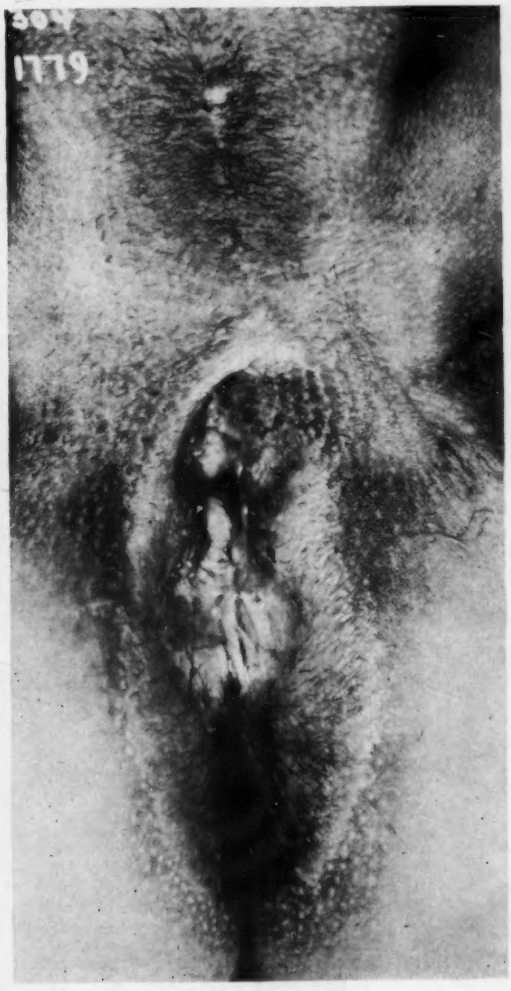

Fig. 4.

Fig. 3.—Same patient as shown in Fig. 2, six months after tattooing (see Fig. I).

Fig. 4.—Pretattoo appearance of anogenital area after four vulval operations for recurrent kraurosis vulvae with pernicious pruritus (see Figs. J and K).

Systemic and general dematologic lesions having anoperianal representation are always appropriately treated and, if possible, eliminated prior to tattooing.

The presence of inflammatory or infectious disease of the anorectum or colon contraindicates tattooing. Lesions, such as anal ulcers, suppuration, fistulas, and hemorrhoids, which apparently are caused by inflammation or

*Progynon B supplied for research purposes by the Schering Corporation, Bloomfield, N. J., through Dr. W. H. Stoner.

infection of the anal glands, the pre-formed anal ducts, and the anal crypts should be eradicated surgically prior to tattooing. A contracted anal outlet is etiologically important and should be eliminated.

It has been my policy to perform radical operations on these individuals with respect to excision of perianal skin, especially when redundant folded perianal skin is present. Large, elliptically shaped blocks of skin are removed, but enough integument between wounds is left to prevent postoperative anal stenosis.

Operation and tattooing should never be carried out at one sitting because the primary operation may be adequate for the control of pruritus in many cases, and also because in the presence of open wounds the mercury sulfide may get into the subcutaneous tissues and form mercury proteinate which is soluble and toxic.

TECHNIQUE

Since the details of the technique of tattooing have already been described,[7] only the essential points will be discussed here.* It is important to deposit the mercury sulfide in the corium and to tattoo the anal canal to the mucocutaneous junction along with the circumanal skin for 1 cm. beyond the visible line of demarcation. In the absence of a naturally demarcated zone, the extent of the pruritic involvement should be delineated before the anesthetic is administered. A regional relaxing anesthetic that will last for one hour is satisfactory. The skin to be tattooed is prepared with ether and alcohol as for any anorectal operation and a thin film of petrolatum is applied. The skin should be held taut to obliterate the cutaneous folds and to facilitate

*The technique is well illustrated in a colored motion picture which is suitable for teaching purposes.

Fig. A.—Pretattoo appearance of advanced circumanal cutaneous changes in a patient with intractable anogenital pruritus of over twenty years' duration. Tattooing is effective for this type of lesion.

Fig. B.—Same patient as shown in Fig. A., fifteen months after tattooing of circumanal area which resulted in the disappearance of the anal and vulval pruritus. Note the permanent post-tattoo red stain produced by the mercury sulfide.

Fig. C.—Same patient as shown in Figs. A and B, six years after successful tattooing. (Photograph made July 17, 1947, when patient was almost 80 years old.)

Fig. D.—Pretattoo appearance of anogenital region of patient with pruritus of about five years' duration, but with only minimal skin changes. This type of lesion is as a rule not suitable for tattooing with mercury sulfide (see discussion in the text).

Fig. E.—Same patient as shown in Fig. D., twelve months after experimental tattooing.

Fig. F.—Anogenital pruritus; tattooing of vulva only, failed to relieve the itching. (See Fig. 1 for pretattoo appearance of anogenital region.)

Fig. G.—Same patient as shown in Fig. F., twenty months after extension of tattooing to perianal area which resulted in the disappearance of anogenital pruritus.

Fig. H.—Pretattoo appearance of "hypertrophic" vulvitis with pernicious and intractable pruritus. Note the advanced cutaneous changes with areas of leucoplakia.

Fig. I.—Same patient as shown in Fig. H, eighteen months after successful tattooing. (See Figs. 2 and 3.)

Fig. J.—Appearance of anogenital area three weeks after tattooing of vulva and five days after tattooing of circumanal and perineal regions for recurring kraurosis with intractable pruritus. (See Fig. 4 for pretattoo appearance of anogenital area of this patient.)

Fig. K.—Same patient as shown in Fig. J., appearance of anogenital region fifteen months after successful tattooing. Note the scarred perineum which is but lightly or inadequately tattooed.

Fig. L.—Appearance of unilateral incomplete tattooing (light color and skipped areas) with unilateral recurrent pruritus. The opposite side is well tattooed and nonpruritic.

Fig. M.—Shows superficial perineal fissures which may cause temporary recurrence of pruritus. Note acute dermatitis of vulva which stopped sharply at the line of tattooed perineum.

Note the inadvertent misplacement of Figs. C and L.

FIG. A

FIG. B

FIG. L

FIG. D

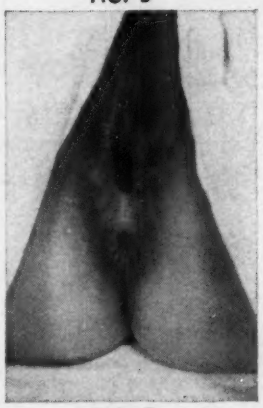

FIG. E

FIG. J

FIG. F

FIG. G

FIG K

FIG. C

FIG. H

FIG. I

FIG M

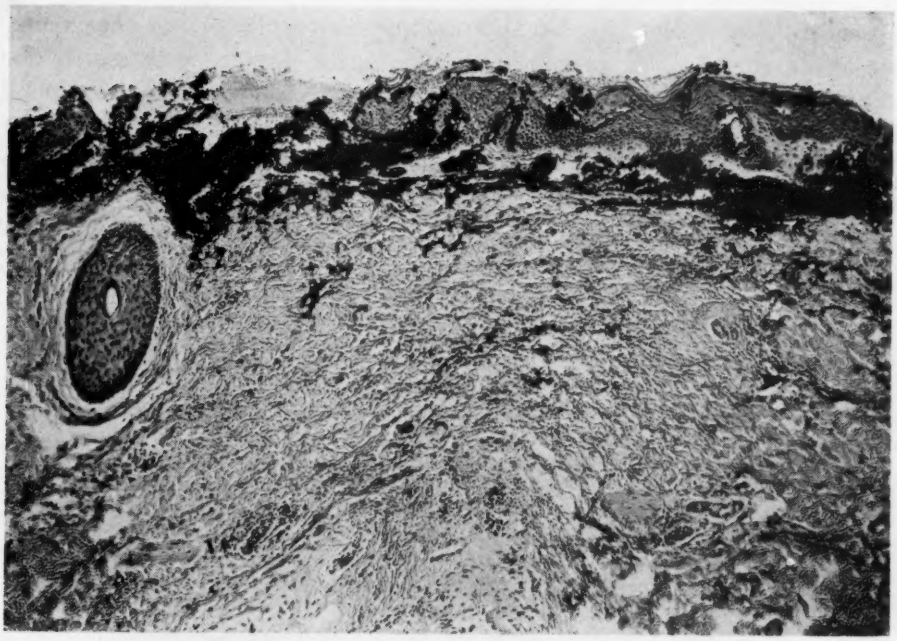

Fig. 5.—Photomicrograph of specimen of tattooed skin obtained immediately after completion of tattooing shows perforations and deposits of mercury sulfide in the epithelium and massive deposition in the upper corium.

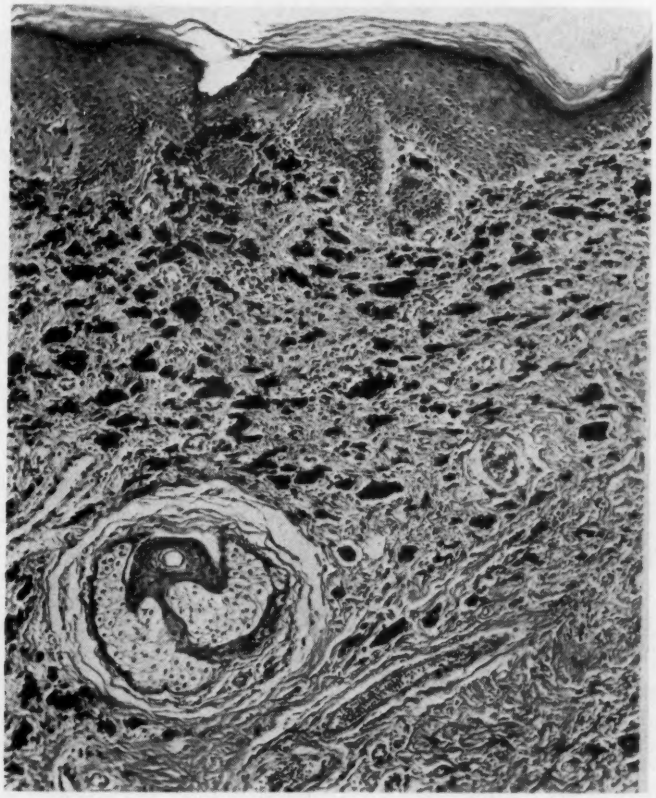

Fig. 6.—Photomicrograph of specimen of skin obtained three months after tattooing shows a subepithelial deposit of clumps of mercury sulfide without evidence of a foreign body giant-cell reaction.

the penetration of the needles and the mercury sulfide into the corium. A paste of mercury sulfide, prepared by mixing the powder with sterile distilled water, is placed on the skin, or the tip of the instrument may be dipped into the paste as often as necessary. The shaft of the instrument should be held at a 45 degree angle or at a right angle to the skin and is advanced slowly, exerting light pressure against the skin; these maneuvers are repeated several times in the same area until the skin shows a uniform and permanent red

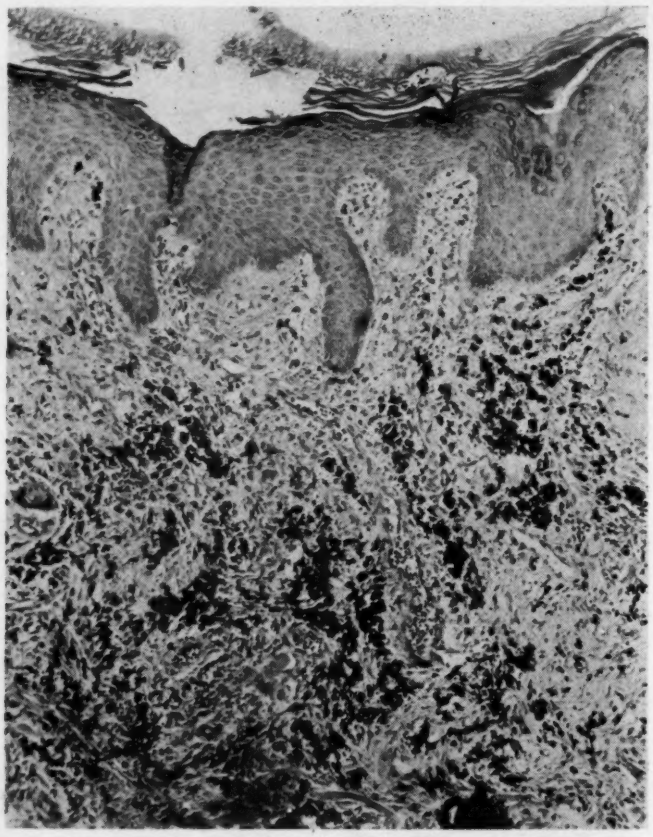

Fig. 7.—Photomicropgraph of a skin specimen obtained eight months after tattooing shows a histologic picture similar to that of Fig. 6.

stain. The speed of tattooing will depend on the type of tattooing instrument employed. The ordinary instrument used by the tattoo artist is satisfactory but makes the procedure extremely tedious and time-consuming. To overcome these objections I have devised a reciprocating (2,000 strokes per minute), pneumatic tattooing pistol utilizing 20 needles in a single row with an adjustable mechanism so that the needles have the necessary protruding travel which varies from 2 to 4 mm. (Fig. 11). With this instrument I am able to do the tattooing for the average case in one sitting in about one hour.

Since the introduction of this instrument the incidence of incomplete tattooing or skipped areas (where localized pruritus may persist and which has erroneously been regarded as a recurrence) has been greatly diminished. Recently I

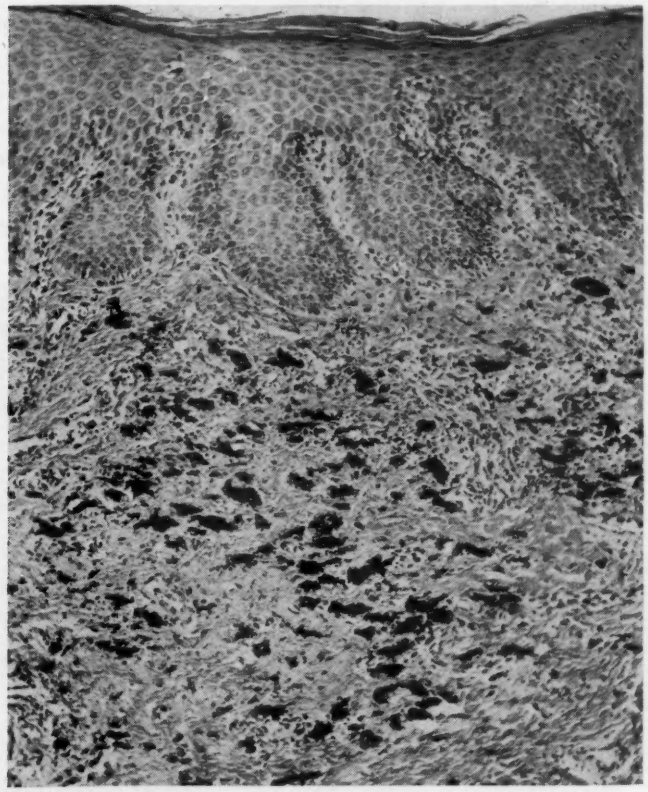

Fig. 8.—Photomicrograph of skin obtained thirty-six months after tattooing shows a histologic picture similar to that observed in Figs. 6 and 7. Again note the absence of a foreign body gaint-cell reaction.

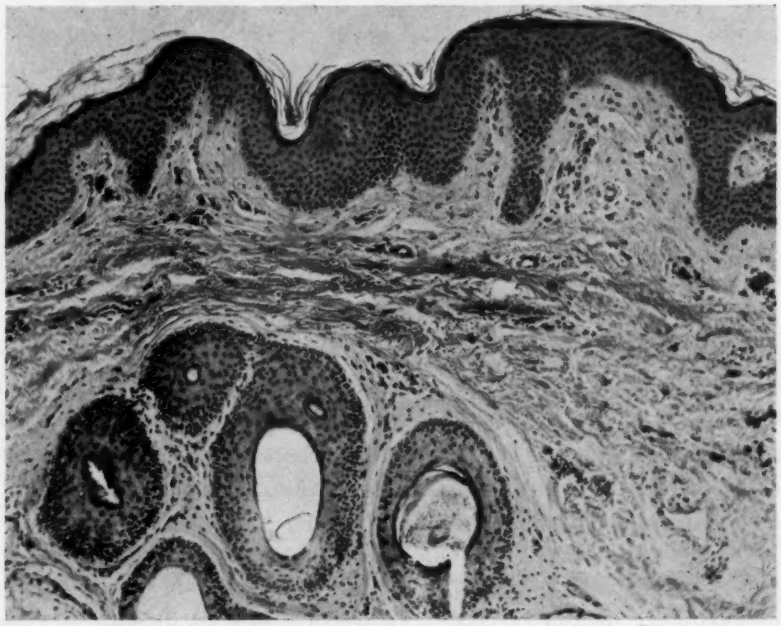

Fig. 9.—Photomicrograph showing a skipped cutaneous area with no or very scant subepithelial deposit of mercury sulfide (see Fig. L.)

have been experimenting with a new effective electric tattooing instrument (Vibro-tool,* Fig. 12). (This instrument is also suitable for tattooing of grafted skin and other phases of plastic surgery.) Following the completion of tattooing, petrolatum gauze is applied. To reduce post-tattoo edema, moist compresses are utilized. Tenderness and moderate pain may persist for about ten to fourteen days and are relieved by moist compresses or sedatives. Desquamation of the tattooed epithelium occurs within a few days after tattooing and re-epithelization ensues in a few weeks.

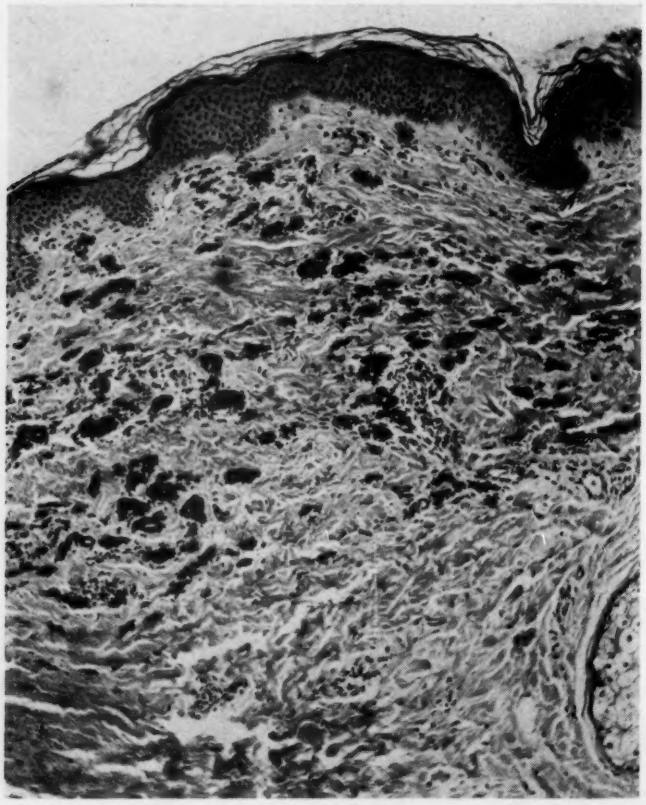

Fig. 10.—Photomicrograph of an adequately tattooed area of skin of the same patient, showing, in contrast, a uniform and abundant subepithelial deposit of mercury sulfide (see Fig. L).

RECURRENCE

Recurrences of anal pruritus in the patient who was considered ideal for this form of therapy have usually been due to inadequate or incomplete tattooing (skipped areas) as shown by gross and histologic studies.[8] This recurrent pruritus promptly disappears following retattooing. Occasionally a pseudo-recurrence may be produced by superficial anal or perineal fissures or suppuration of an anal crypt.

PHYSIOLOGIC PATHOLOGY

The rationale of the tattooing procedure is still undetermined. Personal studies[4] on the mechanism of the action of mercury sulfide deposited in the

*Manufactured by Burgess Battery Co., Chicago, Ill.

corium by tattooing suggest that a functional impairment of the cutaneous sensory terminals is produced which reduces their capacity to respond to adequate stimuli. A change in the cutaneous modalities is produced which apparently is proportional to the quantitative intracutaneous deposit of mercury sulfide.[8] Improvement of the blood supply of the tattooed skin may also play a beneficial role.[9]

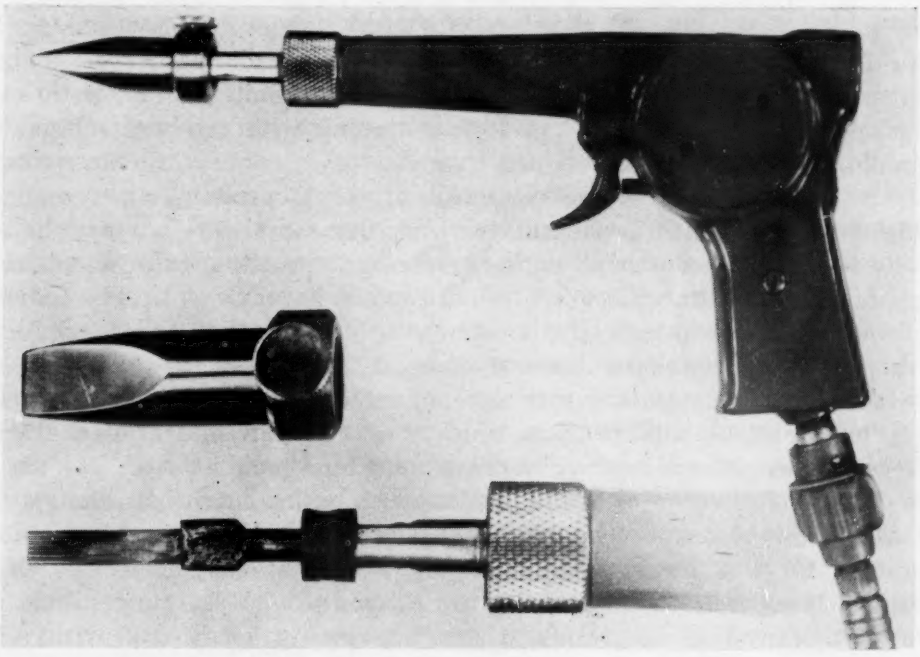

Fig. 11.—Newly developed pneumatic tattooing pistol, assembled and disassembled.

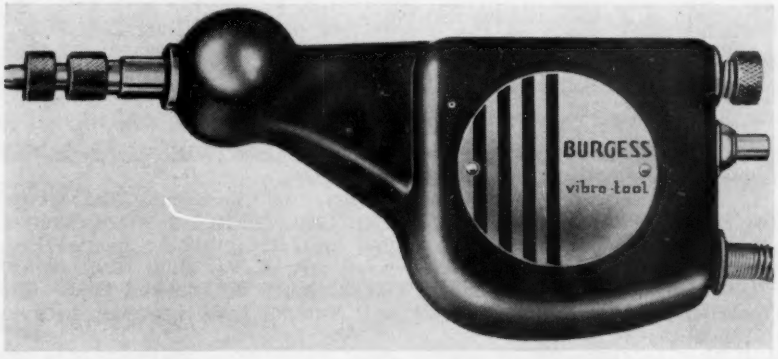

Fig. 12.—The electric Vibro-tool (Burgess) is suitable for tattooing by the addition of a needle holder and an adjusting mechanism as shown in Fig. 11. An even better electric tattooing machine is now in the process of development (Golz).

Mechanical trauma alone as produced by the tattooing instrument without the deposition of mercury sulfide or other chemicals is ineffective in relieving anal pruritus.[4]

Histologic studies of specimens of tattooed skin removed at the conclusion of the tattooing and subsequently at three-month intervals for a period of

over three years have shown no evidence of irritation or of a foreign body giant-cell reaction in the skin similar to that observed after the intracutaneous introduction of other foreign substances. Massive deposition in the epidermis and upper corium is seen immediately after tattooing. Subsequently the mercury sulfide is localized in the corium in various sized clumps which have a slight but definite tendency to reach the deeper portion of the corium (Figs. 5, 6, 7, and 8).[8]

SUMMARY AND CONCLUSIONS

Fifty-five of a group of seventy patients who had had chronic and recalcitrant anal pruritus that was associated with definite characteristic cutaneous changes have responded well to tattooing with mercury sulfide; the remaining fifteen patients obtained "satisfactory" results. Confirmation of this has been obtained in the treatment of vulval pruritus with cutaneous changes. Of twenty-three patients with similar complaints but who had no cutaneous changes consistent with chronic anal pruritus, only six obtained "satisfactory" results while seventeen showed no improvement. This too finds confirmation in the unsuccessful treatment by tattooing with mercury sulfide of vulval pruritus without cutaneous changes.

It appears that tattooing with mercury sulfide is an effective form of treatment for intractable anal pruritus which is associated with definite characteristic cutaneous changes in the absence of anorectocolonic lesions. The patient who complains of severe anal pruritus but who has no cutaneous changes consistent with localized pruritus is, in the majority of cases, an unfavorable candidate for this form of therapy. However, since no deleterious effects have, to date, been observed following tattooing with mercury sulfide this form of therapy may be given a trial in all cases of localized pruritus when more radical procedures, such as the subcutaneous injection of ethyl alcohol or the radical excision of perianal or vulval skin, are contemplated.

Acknowledgment is made of the cooperation of Dr. William Leifer in the dermatologic appraisal of many of these patients.

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CEREBRAL HEMORRHAGE FOLLOWING REPAIR OF A COMMON CAROTID-INTERNAL JUGULAR ARTERIOVENOUS FISTULA

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A REVIEW of the literature, in 1939, by Quattlebaum revealed forty-six cases of common carotid-internal jugular fistulas. When the figures on arterial injuries of World War II are published this number will be greatly augmented. We have been able to find published reports of eighteen other more recent cases, although there are undoubtedly many more we have failed to find. (We have also found reports of some seventeen internal carotid-internal jugular arteriovenous fistulas.)

Quadruple ligation has been the general method of attack in these lesions but more recently there has been an increasing effort to restore the continuity of the artery despite the greater technical difficulties, in an endeavor to prevent cerebral anemia which so frequently occurs following ligation.

Interruption of the common, and especially of the internal carotid has long been known to be hazardous. In Zimmerman's series of 70 ligations of the common carotid there were 26 per cent with cerebral symptoms; in Pitz' series of 600 cases there were 32 per cent.[10] It is generally believed that in older people the danger from this procedure is greater, although Reid and others contended that it is equally dangerous in the young. (We have had the experience of a hemiplegia in a boy 9 years of age following common carotid ligation.)

In fifty cases of common carotid-internal jugular fistula found in the literature there were thirty-three cases where the arterial flow was interrupted by ligation of the artery and vein and seventeen cases in which the artery was restored. In the latter there was a cure of the lesion with no complications except in one patient who died of pneumonia on the eleventh postoperative day. Seven of the successful cases were patients over 40 years of age. Two had evidence of peripheral vessel damage, and two had positive serology. Six had evidence of cardiac damage. Three had evidence of cerebral anemia before operation, including one case of eleven months' duration. The duration of the lesions ranged from ten hours to thirty-seven years. The methods of repair included ligation of the fistula and suture of the opening in the artery from the outside. In most cases the vein was not restored.

In the cases where the artery was not restored but ligated there were two deaths and three recurrences. (In these cases only the artery was ligated.) There was also one death six days postoperative from coronary occlusion. One of the deaths occurred in a 20-year-old individual only eight days after the appearance of the fistula. The other was of eighth months' duration in a 59-year-old person. Both deaths resulted from cerebral anemia. The other patients were cured. They were mainly young individuals, although there were patients 37 and 45 years of age. Most of these were of at least several months' duration. One case showed evidence of cardiac decompensation. One boy of

Received for publication, April 17, 1947.

19 years had a quadruple ligation of the artery and vein only nine days after the appearance of the fistula but he had several frontal headaches for ten days postoperatively. There was one case of hemiplegia in an early ligation of the carotid.

Quadruple ligation was the usual procedure in this series. Although there was a high incidence of success in these cases where the arterial flow was interrupted, most of them had been cases which had responded well to testing before operation by occlusion of the involved vessels by pressure or had compressive exercises before ligation was attempted. One patient with quadruple ligation complained of headaches postoperatively.

TABLE I. COMMON CAROTID-INTERNAL JUGULAR ARTERIOVENOUS FISTULAS—RESTORATION OF ARTERIAL FLOW

LOCATION	REF. NO.	AGE (YR.)	DURATION	TYPE OF REPAIR	RESULTS	REMARKS
1. Rt.	2	N. S.	30 days	Lig. of fistula	Cure	Had cerebral symptoms before op.; no evidence of cardiac involvement
2. Lt.	2	N. S.	3 mo.	Lig. of fistula and vein	Cure	No cardiac involvement
3.	2	N. S.	N. S.	Transvenous suture of arterial opening of fistula; lig. of vein	Died of pneumonia 11th day	Sensory aphasia before op.
4. Lt.	2	58	11 mo.	Lig. of fistula and vein	Cure; palpable temporal artery	Cerebral symptoms preop.; cardiac enlargement
5.	3	58	23 mo.	Restoration of artery	Cure; artery patent after 10½ yr.	
6.	3	55	37 yr.	Vein lig. proximal and distal; transvenous suture of artery	Cure for 2 yr. then arterial aneurysm developed	Short of breath and vessels calcified (before op.)
7.	2	25	1 mo.	Lig. vein transvenous suture of artery	Cure	
8. Rt.	14	46	30 yr.	Lig. of fistula	Cure	Preop. cardiac enlargement
9. Rt.	14	21	6 yr.	Lig. of fistula	Cure	Preop. cardiac enlargement
10. Lt.	7	28	22 days	Restoration of artery and vein	Cure	No cardiac envolvement
11. Rt.	7	40	2 mo.	Restoration of artery and vein	Cure	Slight cardiac enlargement; neg. B. W.
12. Rt.	7	41	30 days	Restoration of artery and vein	Cure	Pos., B. W., preop. cardiac enlargement
13. Rt.	16	33	1½ mo.	Restoration of artery and vein	Good pulse in artery	No cardiac involvement; syphilis
14.	8		N. S.	Lig. of vein; suture of fistula	Cure	Damage peripheral vessels
15. Rt.	9	23	5½ mo.	Lig. of vein; suture of fistula	Cure; good temporal pulse	
16. Rt.	9	24	4 mo.	Lig. of vein; suture of fistula	Cure; good temporal pulse	Fistula 1 cm. in diameter
17. Rt.	9	19	7 mo.	Lig. of vein; suture of fistula	Cure; good temporal pulse	Fistula 1 cm. in diameter

TABLE II. COMMON CAROTID-INTERNAL JUGULAR ARTERIOVENOUS FISTULAS—INTERRUPTION OF ARTERIAL FLOW

	LOCATION	REF. NO.	AGE (YR.)	DURATION	TYPE OF REPAIR	RESULT	REMARKS
1.	Rt.	4	59	8 mo.	Lig. of artery	Death	Shortness of breath before op.
2.	Lt.	4	20	8 days	Lig. of artery	Hemiplegia and death	Shortness of breath before op.
3.		4	30	N.S.	Erosion of aneurysm	Cure	
4.	Lt.	4	25	1 yr., 8 mo.	Lig. of artery	Recurrence	
5.	Rt.	4	16	3½ mo.	Quad. lig. of artery and vein	Cure	
6.		4	N.S.	N.S.	Quad. lig. of artery and vein	Cure	
7.	Rt.	4	25	N.S.	Excision of aneurysm	Cure	
8.		4	N.S.	N.S.	Lig. of artery above and below fistula	Cure	
9.	Lt.	4	22	N.S.	Lig. of artery above and below fistula	Failure; aneurysm still present	
10.	Lt.	4	37	7 yr.	Quad. lig. of artery and vein	Cure	
11.		4	45	N.S.	Lig. of artery distal to fistula	Cure	
12.		4	N.S.	N.S.	Lig. of artery distal to fistula	Recurred	
13.		4	29	N.S.	Partial excision of aneurysm	Cure	
14.	Rt.	4	N.S.	N.S.	Excision of anuerysm	Cure	
15.		4	N.S.	N.S.	Excision of anuerysm	Cure	
16.	Lt.	4	25	N.S.	Quad. lig. of artery and vein	Cure	
17.	Lt.	4	N.S.	2 mo.	Excision of aneurysm	Cure	
18.	Lt.	4	21	1 mo.	Partial lig. of artery; suture of opening in sac	Cure	
19.	Lt.	4	25	2 days	Lig. of common, external and internal carotid	N.S., presume cure	
20.		2	N.S.	N.S.	Quad. lig. of artery and vein	Cured	Headaches preop.
21.	NS	3	10	14 mo.	Occlusion of common carotid distal to lesion with fascia; lig. of vein proximal and distal	Cured; observed 3 yr. and 8 mo. postoperatively	
22.	Lt.	10	22	1½ yr.	Quad. lig. of artery and vein	Cure; no cerebral symptoms	Preop. shortness of breath
23.	Lt.	18	young (7 cases)	N.S.	Main. quad. lig. of artery and vein	Cure	
24.	Rt.	1	19	9 days	Quad. lig. of artery and vein		
25.		15	N.S.	3 mo.	Excision of aneurysm	Cure	Compression exercises
26.	Lt.	12	40	15 yr.	1st stage clearance of veins and applications of bands on vein and artery; 2nd stage transvenous suture of arterial opening	Improved Died 6 days later of coronary occlusion	Cardiac enlargement; syphilis

TABLE III. ARTERIOVENOUS FISTULA BETWEEN INTERNAL CAROTID AND INTERNAL JUGULAR VEIN—INTERRUPTION OF ARTERIAL FLOW

LOCATION	REF. NO.	AGE (YR.)	DURATION	TYPE OF REPAIR	RESULTS	REMARKS
51. Lt.	4	25	3 mo.	Lig. of external carotid, internal carotid, and internal jugular	Cure	
52.	4	21	N.S.	Quad. lig. of artery and vein	Cure	
53. Rt.	4	28	N.S.	Lig. of internal carotid	Improved	
54. Lt.	4	27	N.S.	Quad. lig.	Cure	Weakness in right side
55. Rt.	4	N.S.	N.S.	Lig. of external, internal, and common carotid and internal jugular vein	Cure	
56. Rt.	4	29	8 mo.	Lig. of internal and common carotid and internal jugular vein.	Cure	
57. Lt.	4	N.S.	1½ mo.	Lig. common carotid	Cure	
58. Rt.	18	Young	N.S.	Quad. lig.		

In the repair of carotid-jugular arteriovenous fistula certain complications have been noted. As has been mentioned when the artery has been ligated, cerebral anemia with hemiplegia and death may occur. When the artery is restored, bleeding at the suture line or thrombosis of the vessel may result. We wish to report a case illustrating a complication of arterial restoration which we hitherto have not seen reported in the literature, a case of cerebral hemorrhage following repair of the artery.

TABLE IV. ARTERIOVENOUS FISTULA BETWEEN INTERNAL CAROTID AND INTERNAL JUGULAR VEIN—RESTORATION OF ARTERIAL FLOW

LOCATION	REF. NO.	AGE (YR.)	DURATION	TYPE OF REPAIR	RESULTS	REMARKS
61.	12	Young	N.S.	Transvenous repair of artery; lig. of vein	Cure	
62.	17	53 yr.	3 mo.	Occlusion of fistula tract	Cure	Minimal evidence of cardiac damage

REPORT OF CASE

C. B. B., a 49-year-old white man, a stock farmer, was admitted to the John Sealy Hospital on July 16, 1946, with the chief complaint of a "thumping" in the neck. When he was 12 years old he had fallen and struck the neck on a rock; since that time he had been conscious of a "whirling" sound in the head. It seemed to be accentuated by exercise or excitement. About three years before admission a swelling appeared in the left side of the neck. Beginning three months before, the patient noticed increasing shortness of

TABLE V

	NUMBER OF CASES	RESTORATION OF ARTERIAL FLOW	RESULTS	INTERRUPTION OF ARTERIAL FLOW	RESULTS
Common carotid-internal jugular	50	17	Cure in all cases except 1 death from pneumonia on 11th P.O. day	33	2 deaths hemiplegia; 3 recurrences; 1 death from coronary occlusion
Common carotid-internal jugular	13	2	All cured	11	All cured

breath on exertion, after meals, and on awakening from exciting dreams at night. There was palpitation of the heart at times and a mild cough. In recent weeks he had noticed some swelling of the ankles during the day. History was otherwise noncontributory.

Physical examination revealed a large man, 6 feet 2 inches tall, weighing 162 pounds. There was a fullness of the neck extending from the clavicle to the angle of the jaw. About two inches above the clavicle in line with the great vessels of the neck there was a small indefinite pulsating tumor. A palpable thrill accentuated during systole was noted over the area. On ausculation a harsh continuous murmur with a louder systolic element could be heard. This was transmitted up into the neck and down into the chest, the greater volume being found in the latter. On reclining, the veins of the neck and forehead were quite distended but this was not seen in the erect position. The retinal veins as seen by the ophthalmoscope were thought to be distended. The patient exhibited a Corrigan type of pulse with a rate of 81. Blood pressure was 140/68. Respirations were about 20. The heart appeared to be enlarged by percussion; the apical beat was noted in the sixth left interspace at the midclavicular line. There was a positive Duroziez' sign. There was an aortic diastolic and systolic murmur. The liver was slightly enlarged. Blood pressure changes were still present. Fluoroscopic examination showed a slowing of the heart with increased dilatation on pressure over the fistula. Venous pressure in the left arm was 18.75 cm. of saline solution and 16.25 cm. in the right arm. Vital capacity was 2,750 c.c.

Roentgenograms of the chest for cardiac size showed an enormous enlargement of the cardiac silhouette. The transverse diameter of the heart was 20 cm. as compared to the transverse thoracic diameter of 31 cm. The heart was globular in shape and dilated in all diameters. The lung fields showed marked increase in the vascular markings and pulmonary artery trunks compatible with left-sided heart failure. Skull films were normal except for a suggestion of some decalcification of the dorsum sellae. Electrocardiograms showed evidence of definite myocardial damage.

Laboratory studies showed a negative blood Wassermann test. Urinalysis revealed specific gravity 1,024, acid reaction, protein 1 plus, sugar negative. Microscopic examination showed 10 white blood cells per high power field and rare hyaline cast. Hematology revealed red blood cells, 5,040,000; hemoglobin, 13.9 Gm., or 90 per cent leucocytes per cubic millimeter. Polymorphonuclear leucocytes, segmenters 58 per cent, stags 3 per cent, lymphocytes 30 per cent, monocytes 7 per cent, and eosinophiles 2 per cent.

A diagnosis of arteriovenous fistula between the left common carotid and internal jugular was made. Aug 14, 1946, the patient was operated upon. Before going to the operating room he got up, shaved himself, and said he was feeling fine. He talked very intelligently and rationally in the operating room and moved himself from the stretcher carriage onto the operating table. He was given a local infiltration anesthetic of ¼ per cent procaine with epinephrine. A vertical incision was made along the anterior border of the left sternomastoid, and an arteriovenous fistula between the second portion of the left common carotid and the internal jugular vein was easily exposed. The veins of the neck were greatly distended and the jugular sacculated at the level of the fistula. The artery had been cut transversely through one-half of its width at the original injury. The opening into the sacculation was large. The jugular vein was ligated proximally and distally to the fistula with plain catgut and the carotid artery was temporarily occluded with rubber-shod bulldog clamps. When the artery was freed, the patient complained of pain and was very apprehensive. He was given cyclopropane and oxygen. The vein was then opened and a fresh blood clot removed from the sac. The fistulous opening was then closed through the vein opening. The borders of the arterial opening were brought together from above downward in an end-to-end manner using interrupted fine chromic catgut sutures. The sac was trimmed off close to the first row of sutures, and a second layer of similar sutures was placed in the area. A segment of vein was then closed over this. The clamps were removed and a pulse was immediately felt in the carotid distal to the fistula and in the corresponding temporal artery. The patient did not require any anesthetic for the last thirty-five minutes of the operation and was thought to be in good condition at the end of the procedure. He was returned to the ward at 10:30 A.M. About 3:00 P.M. the patient was seen in the ward by one of us and was

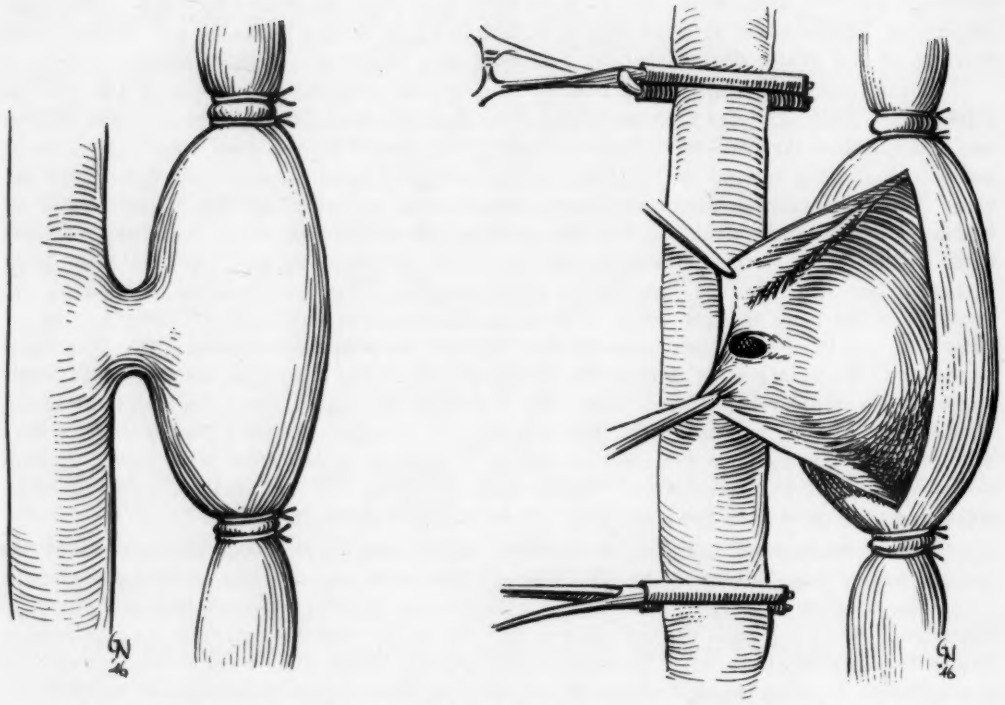

Fig. 1.—Illustrating arteriovenous fistula between carotid artery and jugular vein.

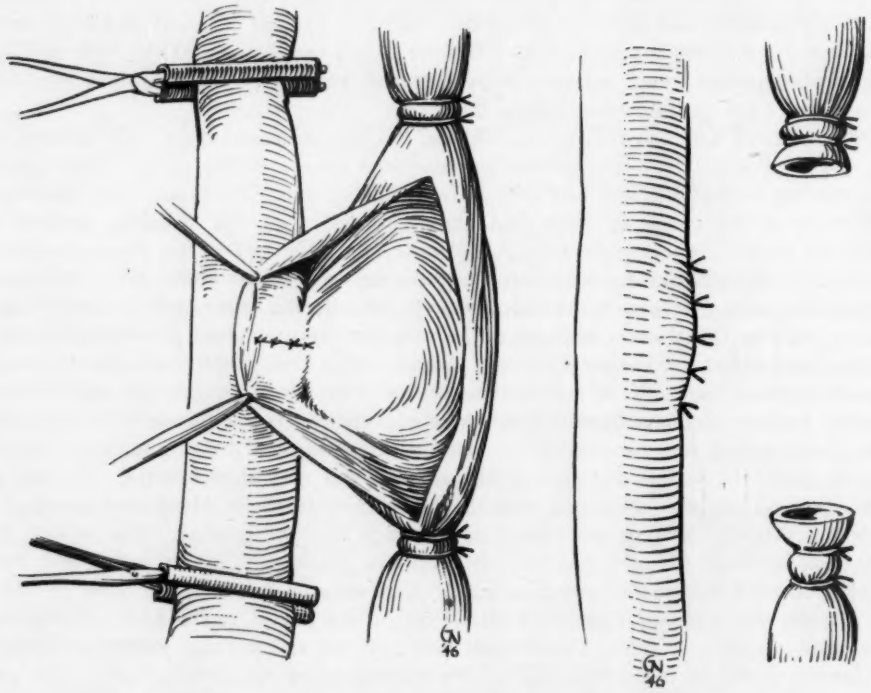

Fig. 2.—Illustrating repair with reconstruction of the artery.

found still sleeping soundly. Blood pressure, pulse, and respirations were normal. All attempts to arouse him were futile. Reflexes were normal but the muscles flaccid. It was felt that he had had a cerebrovascular accident. Thirty cubic centimeters of heparin in 1000 c.c. of 5 per cent glucose was started but within thirty minutes and before 100 c.c. of this solution had been given the respirations ceased and all attempts to resuscitate him failed. He was pronounced dead at 4:45 P.M. and it was felt that a thrombus was the most likely cause of this situation.

Autopsy Findings.—At autopsy it was found that the arterial repair in the neck was intact without thrombosis and that the patient had had a hemorrhage from the left ventriculostriate artery with a large intracerebral blood clot, 6 cm. in diameter in the left temporoparietal region with fresh clots in the entire ventricular system and subarachnoid space, and that the cause of death was evidently the cerebrovascular hemorrhage. On examination of the brain it was found that it weighed 1,520 Gm. The heart weighed 550 Gm. and showed marked hypertrophy and dilatation.

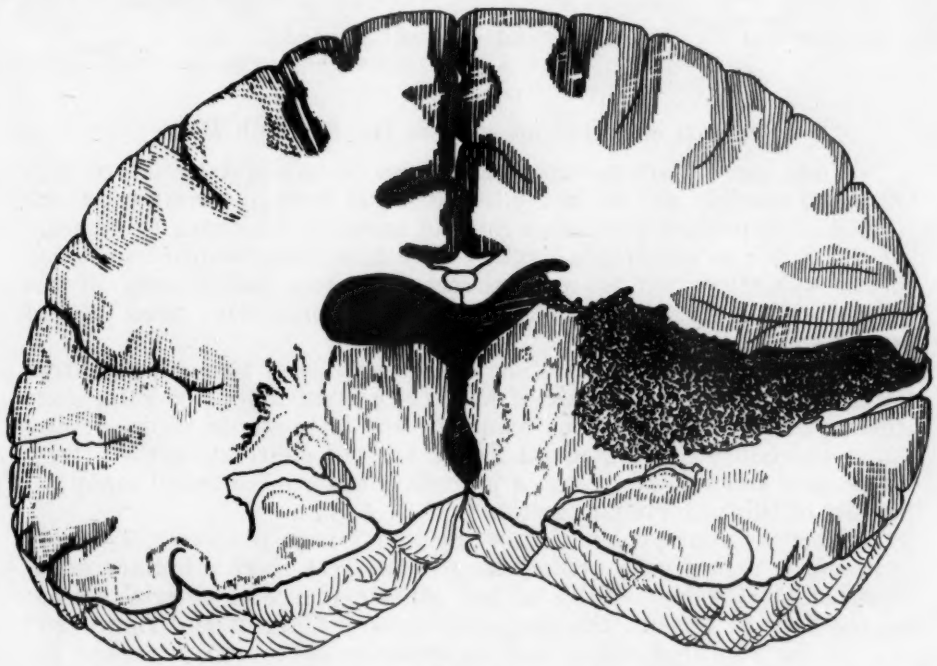

Fig. 3.—Drawing of cross section of the brain showing intracranial hemorrhage which immediately followed reconstruction of the carotid artery.

DISCUSSION

This case showed the classical picture of arteriovenous fistula with the typical thrill and murmer, the slowing of the pulse on occluding the fistula, and the cardiac decompensation that comes on as the lesion persists over a period of time.[11] The points made by Holman recently in regard to the physiologic changes involved in closing the fistula were well illustrated here. When the increased blood volume which was formed to compensate for the leak of the arterial blood through the fistula was suddenly all forced into the arterial system by the closure of the shunt, the blood pressure rose with dilatation of the heart and aortic arch as was observed fluoroscopically. This acting on the end organs of the depressor nerve caused a reflex slowing of the heart with a reduction in blood pressure.

The administration of atrophine by blocking the vagus pathway abolished the slowing of the pulse usually resulting from occulusion of the fistula and the blood pressure did not fall. It was of interest to note here that pressure over the fistula caused the patient to have a headache. This represented an occlusion of the carotid artery rather than the fistula alone. There was no evidence of arteriosclerosis in this patient. The blood Wassermann was negative.

We have assumed that a blood vessel which was formerly carrying a smaller blood volume under a lower pressure was unable to stand the increased load upon it with restoring the carotid artery, resulting in the rupture of the artery in the brain. We were unable to demonstrate any pathology in the artery itself which would predispose to the fatal hemorrhage.

In our zeal to prevent anemia of the brain we restored the artery rather than occluding it by ligation. The procedure was correctly carried out but the fatal outcome was the opposite to what was anticipated.

COMMENT

(Personal communication from Dr. Rudolph Matas)

Your case of arteriovenous aneurysm is indeed very interesting, rare and possibly unique in the literature, at least in the way it terminated. It is possible that other cases of apoplexy following extirpation of the fistula or quadruple ligature may have been recorded in which death was attributed to cerebral ischemia from insufficiency of the Circle of Willis, as is common enough in dealing with pure arterial aneurysms.

But that death should follow the restoration of the cerebral circulation by conservative repair of the artery must indeed be rare, since the cure of an arteriovenous fistula by the transvenous route, or any other procedure that closed the fistula without obliterating the artery, is too new and relatively rare a procedure to have furnished many examples of this unfortunate accident.

I believe your explanation of the hemorrhage is correct. The only question is regarding a predisposing cause. Was there a miliary aneurysm of the Circle of Willis or any other evidence of arterial disease in the finer arteries of the apoplectic zone of Charcot and Bouchard?

If the ruptured artery and its branches have been preserved for careful histologic changes it is more than probable that a weak spot of atheroma or arterial degeneration is found to be responsible for the hemorrhage. Your case is another example of the fact that the cure of an aneurysm sometimes kills the patient, as happens when an aneurysm of the caeliac axis of the aorta is spontaneously obliterated by coagulation, owing to the necrosis of the liver and duodenum by ischemia; likewise, when an aortic aneurysm is obliterated at the renal origin.

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LOBECTOMY FOR PULMONARY CYSTS IN A FIFTEEN-DAY-OLD INFANT WITH RECOVERY

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(From Temple University Medical School)

PRIOR to December, 1946, the youngest patients with pulmonary resection were reported by Fischer, Tropea, and Bailey[1] and by Gross.[2] The patient described by Fischer and his associates was 30 days old and the lesion was a large thin-walled pulmonary cyst with bronchiolar mucosa and musculature. The cyst involved the right upper and middle lobes. The follow-up for one year after lobectomy showed normal growth and development with a most satisfactory x-ray appearance of the chest. Gross's recent report was of an infant 23 days old. In this case the congenital cyst involved the upper lobe and extended into the hilar region which necessitated pneumonectomy rather than lobectomy. Follow-up in this case was for six months and the child's progress was excellent.

The case which we are reporting describes a 15-day-old infant with a similar clinical and pathologic picture; this is the youngest patient on record in whom a pulmonary resection was performed. We feel that these cases are of particular interest in that they show the feasibility of major pulmonary surgery in infants suffering with congenital pulmonary air cysts which often indicate a very poor prognosis.

CASE REPORT

Baby U. B. W., female, was born May 4, 1945. She was admitted to Temple University Hospital May 18, 1945, and discharged June 2, 1945.

History.—The chief complaint was of marked dyspnea. The mother stated that the child was apparently normal from birth until five days before admission when dyspnea began and persisted. Four days later this became quite severe, and cyanosis appeared. A physician was consulted who admitted the child to a local hospital. Roentgenograms were made which revealed multiple loculations of air in the left side of the chest which appeared to involve the entire hemithorax and displace the heart and mediastinum markedly to the right. The multiple loculations of the air in the left side of the chest were interpreted as representing stomach and intestinal contents and an area of density in the lower portion of the chest was interpreted as spleen, so that a diagnosis of diaphragmatic hernia was erroneously made. This same evening the patient was transferred to Temple University Hospital.

Physical Examination.—The child was markedly dyspneic and cyanotic, and the respirations were extremely shallow, excessively rapid, and grunting in character. There was retraction of the supraclavicular spaces on inspiration. The left side of the chest was tympanitic with absence of voice and breath sounds. Breath sounds could be heard only in the right axilla and in this region some alveolar râles were also noted on inspiration. The heart was completely displaced into the right side of the chest, and there was a pulse rate of 160 per minute with a suggestion of quadruple rhythm. The abdomen revealed no masses, the liver was normally palpable, and one observer thought that the spleen could be palpated. Peristalsis was present in the abdomen but not in the chest. The umbilicus was recently

Received for publication, March 6, 1947.

healed with no evidence of infection. The extremities were negative, reflexes were normal, and the skin showed a normal turgor. The temperature was normal, and the blood showed 15 Gm. of hemoglobin, 5,300,000 erythrocytes, and 17,800 leucocytes with 70 per cent polymorphonuclears, 47 per cent of which were nonfilamented.

Hospital Course.—The admitting diagnosis of "hernia, diaphragmatic, left, congenital" was accepted on the basis of the symptoms and the x-ray films showing the multiple loculi of air, which were interpreted as intestine, in the left side of the thorax. Because the child's condition had grown rapidly worse in the first few hours after admission and she was unable to take feedings, it was felt there was no time for further study and at 11:00 P.M. on the day of admission, May 18, 1945, laparotomy was performed. Although a thoracic approach was considered, it was discarded in favor of the less shocking left upper rectus approach under local anesthesia with oxygen inhalation. However, at operation it was found that both diaphragms were intact that it was then realized that the pathology was that of a

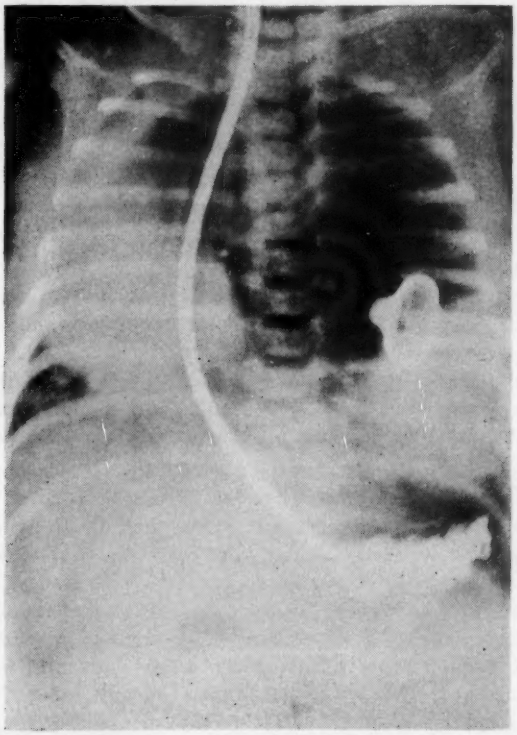


Fig. 1.—Roentgenogram of chest after laparotomy and insertion of mushroom catheter in left side of chest. (Note marked displacement of heart and mediastinal structures and compression of right lung; stomach situated in normal position.)

congenital pulmonary cyst on the left. The abdominal incision was closed. Fearing further major surgery at this time, a needle was inserted into the left side of the chest. Pressure readings varied from plus 5: plus 30 to plus 4: plus 6. After removal of 100 c.c. of gas, there was a temporary decrease in positive pressure and corresponding slight improvement in respiration. In an effort to avoid the return of positive pressure, a stab wound was made deeply into the sixth left interspace and a catheter inserted into the cyst for constant gentle suction. Checking the pressure readings through the catheter revealed the same oscillations as before.

On the following morning, May 19, 1945, there was no appreciable improvement (Fig. 1), and it appeared that the only hope of survival for this infant lay in resection of the involved portion of lung or possibly in the removal of the cyst only, which had been successfully accomplished on several adults previously.

At 2:00 P.M. on this, the day after admission, under field block anesthesia with ¼ per cent metycaine and positive pressure oxygen by mask, the catheter was removed and an incision was made along the left fifth interspace. The interspace was opened, and the ribs spread with a thyroid retractor. The left upper lobe seemed normal, but the lower lobe was completely diseased, consisting of multiple air cysts in its cephalic half and of firm induration at its base. The lobe was freed from soft adhesions, and dissection was begun on the hilus, but was discontinued because of the patient's poor condition, and a No. 1 chromic ligature was tied about the hilus. Distal to this a transfixion suture of No. 00 chromic catgut was applied, and the lobe was amputated just beyond this point. A flap of pleura was then developed from the posterior chest wall and hinged over the stump. The upper lobe was re-expanded by positive pressure, indicating that the upper lobe bronchus was not obstructed, and 25,000 units of penicillin and a few crystals of sulfanilamide were placed in the pleura. The ribs were approximated with pericostal sutures of No. 1 chromic catgut, each of the two layers of overlying muscle with No. 00 chromic, and the skin and subcutaneous fascia with a continuous lock stitch of No. 35 alloy steel wire. A stab wound was then made in the seventh interspace and a No. 18 French mushroom catheter inserted. By means of positive pressure on the mask and slight suction on the tube, the intrapleural pressure was brought to within normal limits so that there was immediate improvement in the baby's respiratory function. The tube was clamped off and not attached to suction for twenty-four hours to allow the sulfonamides and penicillin to decontaminate the area. There was possible contamination, since one of the thin-walled cysts had ruptured during dissection, and a small amount of mucopurulent material exuded in the field.

Pathology.—Grossly, the apical portion of the lobe appeared to be quite cystic, while in the basilar portion there was considerable induration (Fig. 2). On section it was found that the apical portion contained one large, one medium-sized, and many small air cysts. The indurated basilar portion appeared to be mainly atelectatic with a rather considerable amount of trapped puriform secretions. This material could be expressed from the solid basilar portion into the larger air cysts, indicating their communication. The interior of the cysts showed the fibrillar structure usually visible in pulmonary air cysts.

Pathologic description was as follows: Slides from the consolidated portion of the specimen (Fig. 3, *A*) displayed a maize of channels lined by tall columnar epithelium. Occasionally smaller spaces were found in between which were lined by smaller cuboidal cells. The larger bronchi showed the usual ciliated pseudostratified columnar epithelium. All of the spaces were filled with leucocytes, many undergoing degeneration, giving the exudate a suppurative aspect. Included were many macrophages. Some of these were unusually large, almost giant sized. These were vacuolated, multinucleated, and contained engulfed particles. Inflammatory cells also were found infiltrating the larger bronchial walls, and among these eosinophiles were prominent. There was no fibrosis or any other tissue alteration which would indicate a long-standing process.

Sections of the cystic portion (Fig. 3, *B*) showed a pleura considerably thicker than normal as a result of hemorrhage and edema accompanied by pigment-laden macrophages. The underlying parenchyma contained a slightly greater number of alveoli than seen in the other sections, but dilated bronchioles were still conspicuous. A few macrophages were within the alveolar spaces and bronchial lumens. The inner cyst lining was irregular as a result of papillary projections lined by tall columnar epithelium which were part of bronchioles. The changes observed affecting the bronchial elements were quantitative as well as qualitative. Not only were the bronchioles dilated and filled with exudate, but they exceeded by far the number of alveoli. The paucity of alveoli could not be attributed to obliteration by expanding bronchioles or inflammation since neither atelectasis nor replacement fibrosis were apparent. The bronchiolar increase appeared to be both an absolute and a relative quantity which seemed best explained on a congenital basis. The suppurative exudate was ample proof of an inflammatory reaction. Its nature was nonspecific although the giant cells were unusual and forced the mentioning of the possibility of the so-called "giant-cell pneumonia" seen in infants and thought to be associated with the virus of dis-

SURGERY
VOL. 23, NO. 1, JANUARY, 1948

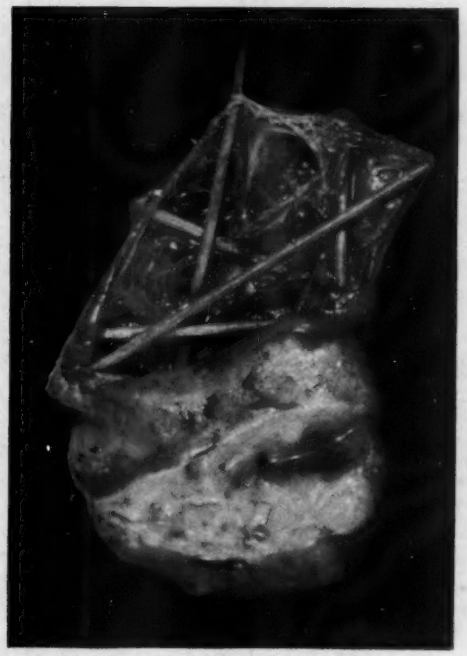
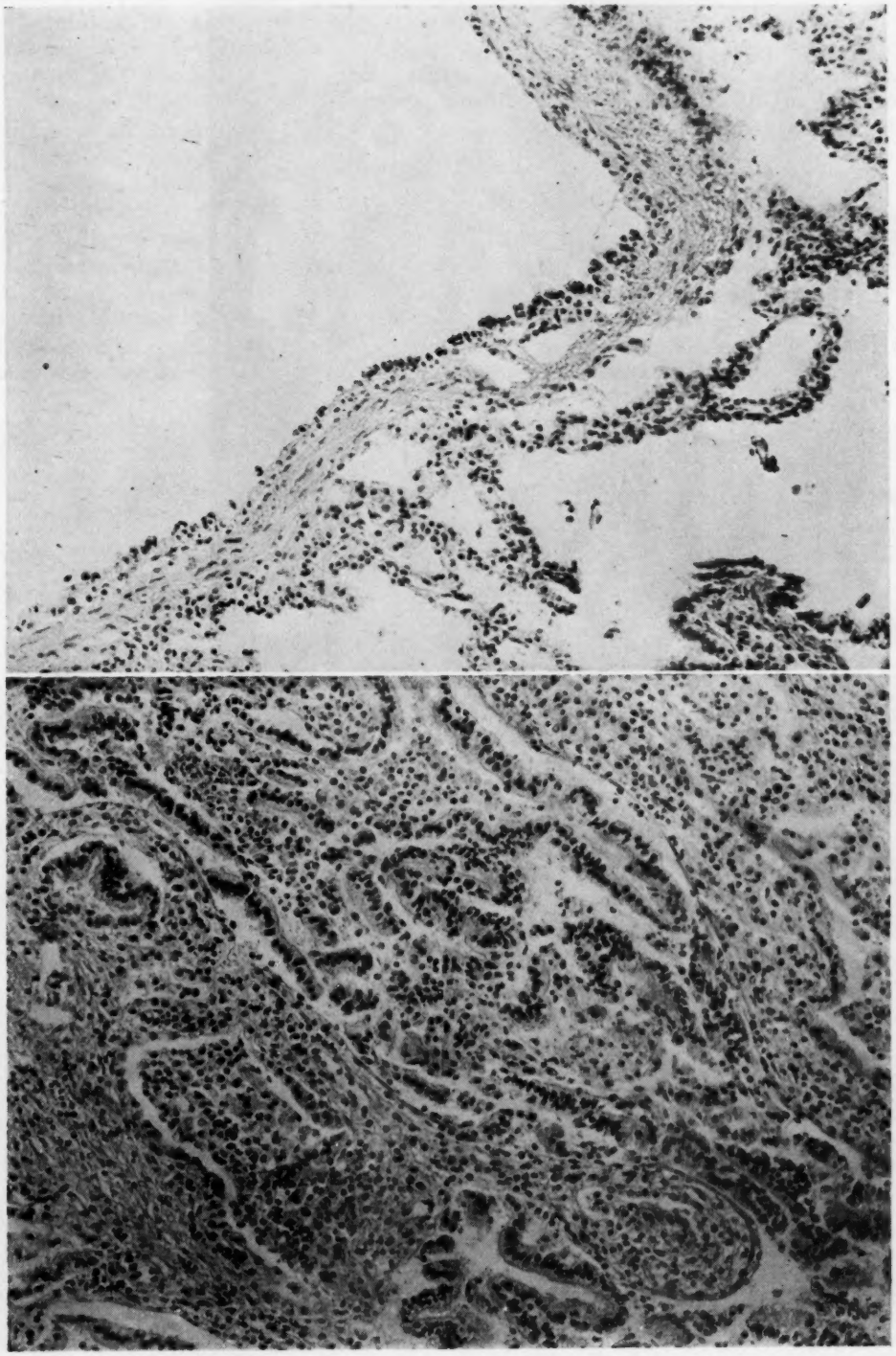


Fig. 2.—Gross specimen, showing the apical cystic portion and also the indurated basilar portion. (Note homogeneous appearance of sectioned basilar portion of this lobe and its resemblance to atelectasis with consolidation.)



B.

A.

Fig. 3.—*A*, Histology of solid portion showing preponderance of bronchial elements with infection causing inflammatory exudate. *B*, Section of cyst wall showing bronchial epithelium lining the cavity.

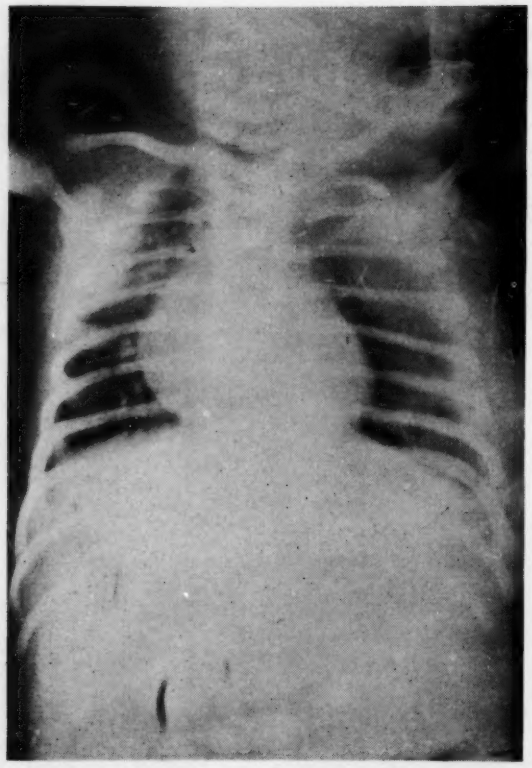


Fig. 4.—Roentgenogram of chest two days postoperatively showing restoration of the mediastinum of the midline and relatively normal expansion of both lung fields.

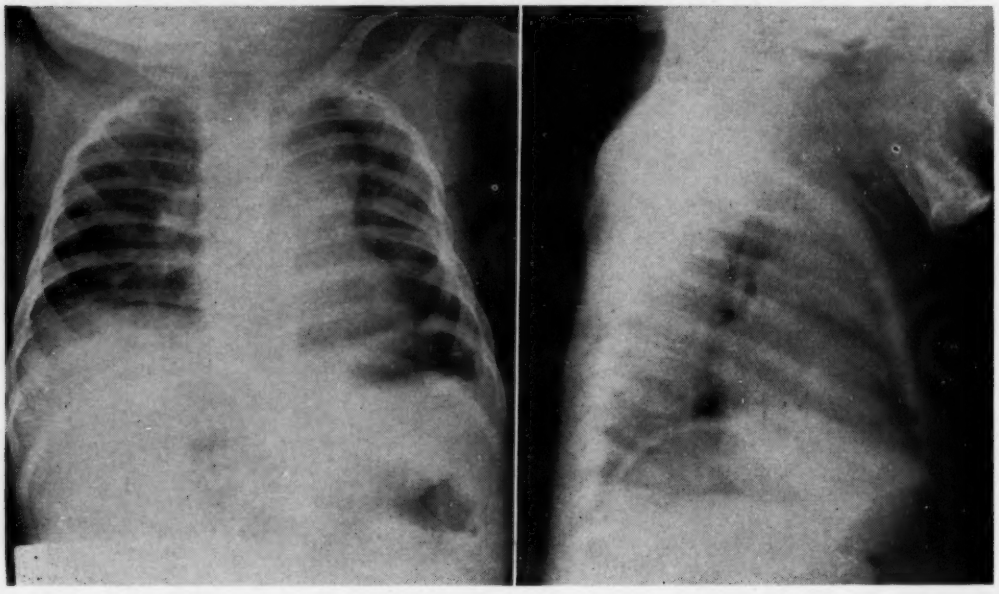


Fig. 5.—Roentgenogram of chest eight months postoperatively showing a normal infant's chest.

temper. Our experience with this particular lesion is admittedly minimal. Breakdown of tissue lipoids can also cause a reaction in which there is the appearance of giant cells.

Obviously the pathogenesis of this lesion was the matter of primary importance and interest. It was felt that there had been abnormal pulmonary parenchymal development, to which had been superimposed a suppurative reaction giving the lesion a dual nature.

Bacteriology.—Cultures from the bronchial stump at the time of operation revealed no growth in five days. Those taken from the puriform material in the congenital cyst were reported as showing an occasional anaerobic *Staphylococcus albus* and a few anaerobic nonhemolytic streptococci.

Postoperative Course.—The postoperative course was most satisfactory. Immediately after operation the patient's condition improved considerably and all dyspnea and cyanosis disappeared within a few hours. On the first two postoperative days the temperature rose to 102.1° F. by rectum from which point it receded gradually until the seventh postoperative day, at which time it became normal and remained so until discharge. The child was given 4,000 units of penicillin intramuscularly at two-hour intervals. Intravenous fluid and blood were continued as indicated through the cannula in the saphenous vein.

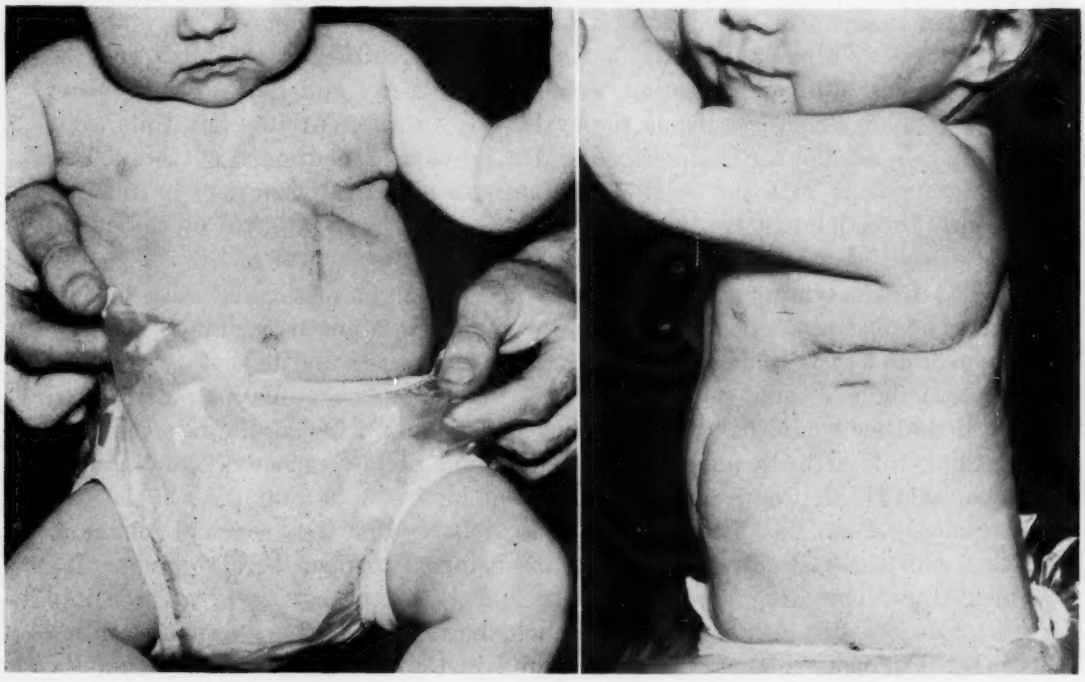


Fig. 6.—Infant six months postoperatively showing normal development.

On the third postoperative day a suppurative thrombophlebitis, involving the area of saphenous canalization, was noted, and culture of this revealed a coagulase positive hemolytic staphylococcus. This responded well to local wet dressings and probably also to the systemic penicillin therapy which was continued for fourteen days postoperatively.

X-ray check-ups, beginning two days following lobectomy (Fig. 4), showed the mediastinal structures to be in the midline, the right lung expanded to normal volume, and aeration of the left upper lobe to be satisfactory. The leaves of the diaphragm moved in phase, and the right was sharply outlined, while that on the left was slightly less sharp and normally situated. The axillary portion of the left side of the chest was obscured by hazy density, representing pleural reaction to the surgical procedure, but by June 1, 1945, the fourteenth postoperative day, the aerated portion of the left lung was more clearly seen, although some pleural thickening was noted about the left base and axillary region with some obscuring of

the costophrenic sulcus. However, the aeration of both lungs appeared satisfactory, and the cardiac silhouette remained normally situated.

The child was discharged from the hospital on June 2, 1945, which was the fifteenth postoperative day, in excellent condition. Both the abdominal exploratory wound and the thoracotomy wound had healed by primary intention. There was no dyspnea nor cyanosis, and the baby was gaining weight in a satisfactory fashion on normal feedings.

Re-examination up to and including sixteen months after surgery revealed a child of normal development without respiratory symptoms or loss of energy. The incisions remained well healed, and x-ray check-ups of the chest showed only slight mediastinal displacement to the side operated upon (Fig. 5).

DISCUSSION

The diagnosis of pulmonary air cyst is not difficult if one is suspicious of such a possibility. As pointed out by Anspach and Wolman,[3] the ease of confusion with diaphragmatic hernia or eventration of the diaphragm can be easily overcome by ingestion of small amounts of barium, demonstrating abdominal viscera in their normal or abnormal position (Fig. 1). Single large cysts may be confused with pneumothorax, but the lowered position of the hilus and the persistence, in spite of aspiration, as well as the x-ray and thoracoscopic views of the fibrillar structures inside the cysts, help to differentiate. Multiple cysts may contain fluid or air as described by the previously mentioned authors. This may confuse one with the possibility of infection, and abscess may be thought present. Infection may confuse the picture as in the cases reported by Rosemond and Caswell[4] of pressure pyopneumothorax in the first month of life.

The urgent symptoms and extremely poor condition of some of these infants militate against prolonged study. However, the ingestion of barium is a simple maneuver and was discussed in this case but erroneously omitted. In retrospect, the gastric bubble could easily be seen below the diaphragm of this patient, and very little time would have been consumed in giving a few swallows of barium. We think this error is unjustifiable and should not be repeated. As in some others, this child progressed normally from birth for several days to become increasingly dyspneic. The explanation is probably that the bronchial communication with the cystic areas is oblique or distorted to form a valvular opening which traps increasing amounts of air to balloon the cavity to greater and greater degree, displacing effective parenchyma until pulmonary decompensation occurs. Further evidence for this is found in the positive pressure within the cysts, the temporary improvement from aspiration or drainage, and the disproportion between the size apparent on x-ray views and that of the removed specimen.

The remarkable ease with which lobectomy can be done in infants was noted in this patient and was described by Fischer and his co-workers and by Gross. The hilus forms a small pedicle, as occurs in dogs, making hilar ligation simple and easy and shortening the operation greatly. It has been possible in several of our patients, both adults and children, to excise cysts or large bullae and conserve the remainder of the lung; while in others, particularly with infection, lobectomy has been required.

Field block anesthesia contributes greatly to avoiding shock in these tiny patients and is extremely satisfactory if combined with slight positive pressure

oxygen inhalation. We were unwilling to intubate the trachea of this small child but have done so in children of a few months of age.

The pathologic description is interesting in that the indurated basilar portion of the removed lobe, which grossly had appeared to be atelectatic lung, was shown on histologic section to display a maize of channels lined by tall columnar epithelium. These channels were no doubt bronchial in origin and represented a similar histologic but a different morphologic picture than was seen in the larger cystic areas in the upper lobe. The presence of the definite inflammatory change is also of interest and brings up the possibility of pulmonary infection, adding to the already severe situation caused by the marked increase in intrapulmonary pressure.

CONCLUSIONS

1. Pulmonary resection for the treatment of congenital pulmonary air cysts in infants is a feasible and lifesaving procedure.

2. The case of the youngest patient with lobectomy on record is described.

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

THE PROBLEM OF PARENTERAL NITROGEN ADMINISTRATION IN SURGICAL PATIENTS*

WITH SPECIAL CONSIDERATION OF PREOPERATIVE PREPARATION AND OF THE MEANS OF EFFECTING FAVORABLE NITROGEN BALANCE

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INTRODUCTION AND STATEMENT OF THE PROBLEM

THE steady decline of surgical mortality rates concomitant with an ever broadening surgical horizon and a more aggressive surgical attack on well-recognized pathologic states has been one of the outstanding achievements of the past ten years. Many factors each contributing their increment of improvement, have played a part in this accomplishment. Better and safer anesthesia, coupled with judicious and adequate replacement therapy during surgery, has allowed the surgeon to do an unhurried and deliberate operation, leaving nothing to chance. Chemotherapy and antibiotics have been invaluable tools in combating infections. But often the issue is decided before the patient goes to the operating room by the type of preoperative preparation he receives. To this end, a broader understanding, on the part of surgeons, of the general problem of protein metabolism and of the necessity of rebuilding the depleted protein stores of the malnourished patient is of real importance.

It is readily conceded that the oral route when it is available to the patient is to be preferred for this type of preparation. However, in not a small group of patients, particularly those with benign or malignant obstruction of the esophagus or gastric outlet, in chronic or subacute bowel obstructions, in external or internal intestinal fistulas, and in the emaciated state of ulcerative colitis, this avenue of alimentation is not available. It is in this poor-risk group where the ravages of malnutrition and starvation are most marked, and where the need for food is most desperate, that one must avail himself of other means of supplying vitally needed protein and calories. In addition there is a large group of patients in whom, for one reason or another, only a substandard amount of food can be assilmilated orally and in whom protein and caloric needs must be augmented by parenteral means.

The researches presented here were supported by the Augustus L. Searle Fund for Experimental Surgical Research, the Berenice Moriarity and Robert Cooper Funds for Surgical Research.

In partial fulfillment of the requirements for the degree of Doctor of Philosophy in Surgery, May, 1947.

It is proposed in this thesis to present the problem of protein metabolism and protein depletion as it relates to surgical patients. The means of supplying to the poor-risk patient by the intravenous route the protein he so desperately needs have been studied. It will be shown that these patients can be maintained in positive nitrogen balance by parenteral feedings alone, and that, if adequately prepared in this fashion, they can withstand operations of major magnitude with risks comparable to the uncomplicated case.

GENERAL CONSIDERATIONS OF PROTEIN METABOLISM AND A REVIEW OF PERTINENT LITERATURE

Historical Development of Concepts of Protein Metabolism.—In recent years there has been accomplished a fulfillment of the original meaning of the word protein, that is, of first importance. This added emphasis has developed slowly, for originally it was assumed that the proteins of the body were in a very stable state and were regarded more as inert structural elements rather than active dynamic participants in the chain of metabolism.

According to the classical theory of Folin[69-71] protein metabolism consists of two phases, one an endogenous phase which is in progress continuously. This corresponds to the amount of nitrogen excreted on a nitrogen-free diet and its marking end product in the urine is creatinine, neutral sulfur, and to a lesser extent uric acid. The excretion of these end products Folin found to be constant for each individual, regardless of the nitrogen intake or the nitrogen output. The other, an exogenous phase, and variable in character, is related to the amount of nitrogen foodstuff ingested and yields as its end product chiefly urea and inorganic sulfur. It was felt that protein synthesis in the adult organism in nitrogen equilibrium is restricted to replacement of the endogenous quota and when more than this minimal quantity of protein is ingested, it is quickly catabolized and appears in the urine chiefly as urea. Earlier Voit[206] postulated that protein of food passed through the blood stream to the tissues where it was catabolized under the influence of living protoplasm without first becoming an integral part of that protoplasm. Pflüger,[158] on the other hand, felt that all protein catabolized must first be transformed into an integral part of living tissues and as such undergoes oxidation.

McCullum,[132] Osborne and Mendel,[153] and Mitchell[144] questioned whether "wear and tear" or endogenous metabolism really involved the destruction of any intracellular protein. The latter felt that Folin's figures prove only that the excretion of creatinine is constant. Endogenous metabolism may be largely suppressed with protein feedings either because, by virtue of the mass action law, retardation of tissue hydrolysis by amino acids being set free by digestion of protein may occur, or from dietary protein catabolism certain nitrogenous substances become available which otherwise might have had to come from tissue protein. Nevertheless, the concept of the protein tissues of the body being in a more or less static and relatively inert state, that nitrogen ingested in excess of that necessary to replace the "wear and tear" of endogenous metabolism could not be stored and was excreted promptly in the urine as urea was generally believed.

In 1935 Borsook and Keighley[20] first proposed their theory of continuing metabolism of protein which is completely in the opposite direction of previous modifications of Folin's theory. They stated that, in an animal in nitrogen equilibrium, the breakdown of intracellular protein is continuously in progress even when abundant quantities of amino acids are obtained from the diet. This breakdown bears no "wear and tear" connotation and is directly proportional to the level at which nitrogen balance has been set by the previous dietary history. As a consequence, in nitrogen balance a corresponding quantity of amino acids is synthesized into tissue protein and peptides. When protein is ingested in the course of the next twenty-four hour period some of its amino acids contribute toward maintaining constant the concentration of free amino acids in the blood and tissues. A large fraction is synthesized into protein and peptides while the remainder is catabolized; this latter appears in the urine. The evidence for this hypothesis is that when nitrogen balance was maintained for one day with nonsulfur-containing amino acids, the sulfur excretion was considerably in excess of the endogenous sulfur excretion. In view of the fact that nitrogen balance was maintained, an increased endogenous metabolism could not be invoked to account for a sulfur excretion in excess of the endogenous level.

In a series of important contributions from Whipple's[53, 99, 103, 128, 159] laboratory, the concept of a "dynamic equilibrium" between the various stores and depots of body protein was developed. Holman and associates[99] first showed that dogs could be kept in nitrogen equilibrium by administering dog plasma intravenously as the sole source of nitrogen intake. The idea was developed that plasma proteins, without being broken up into amino acids, could leave the circulation and be available for the body needs. This concept was extended and confirmed by Pommerenke and co-workers[159] and by Daft and associates.[53] In 1938 Howland and Harkins,[103] in a well-conceived experiment, showed that when a phlorhizinized dog is fed plasma protein orally, the protein is readily digested to amino acids with conversion of 58 per cent of the protein into sugar, and with excretion in the urine of increased amounts of nitrogen and sugar. When the same plasma protein is given intravenously to phlorhizinized dogs, there is no increased urinary nitrogen excretion and no conversion of protein to sugar. This points to a different metabolic mechanism on the part of the body. It was suggested by Howland and Harkins that there is no need for intravenously injected protein to be broken up into amino acids for utilization, but rather that a partial catabolism of the injected protein occurs, with reassembly of the large aggregates performed by the cells to conform to the needs of their own peculiar type of protein. From plasmophoresis experiments[128] it was shown that there is a fairly large store of body protein which, when plasma protein is withdrawn producing hypoprotenemia, can readily be converted into new plasma protein. This reserve store of plasma protein-producing material is part of the general stores of the body. It is a bulwark against infections and toxemia. In its absence little new plasma protein is formed.

Further evidence that larger aggregates than amino acids are utilized by the body is offered by Reineke and associates[164] who showed, in lactating goats, that glycoprotein is used directly as the precursor of the protein of milk.

It was demonstrated for the first time in 1940 by Wangensteen and coworkers[207] and Kremen and associates[113] that, similarly, man could be maintained in positive nitrogen balance by administering human plasma intravenously as the sole source of nitrogen intake.

Schmidt, Allen, and Tarver[183] in 1940 postulated that a synthesis of proteins can take place in the body by transformation of existing proteins into others without being broken down into amino acids first.

The work of Schoenheimer and his associates,[179, 180] using isotopes of hydrogen, carbon, and nitrogen have demonstrated that every protein in the body is continuously changing and renewing its structure. Rapid amino shifts among the amino acids of the proteins of the body were observed. Amino acids of the body other than those administered were found to contain a considerable quantity of isotopic nitrogen. By measuring the concentration of isotopic nitrogen in a tissue at a certain time, an index of the chemical activity of its proteins could be obtained. Serum proteins always contained the highest concentration of isotopic nitrogen, and then in order of magnitude came viscera, muscles, and skin.

To quote Schoenheimer and Rittenberg: [179]

> Results of experiments with feeding isotopic physiological compounds to animals can scarcely be reconciled with the concept of endogenous and exogenous varieties of metabolism. Body constituents are involved in continuous chemical processes and there exists a close correlation between food materials and body components. Peptide, ester, and probably other linkages of the complex body materials open and close continuously. The amino acids, fatty acids, and other units temporarily liberated mix with others of the same species of whatever source, diet or tissue. By this mixing process they become indistinguishable as to their origin. Nitrogen excreted in urine may be regarded as part of the metabolic pool originating from the interaction of dietary nitrogen with the relatively large amounts of reactive body nitrogen, and the same applies to the other groupings of dietary and tissue substances.

In feeding isotopic nitrogen to rats,[181] an equal amount was rapidly recovered from all the fractions of plasma proteins. The proteins of the red blood cell, however, were found to have considerably less isotopic nitrogen, while the heme fraction of the red blood cells contained the least amounts of isotopic nitrogen. This seems to indicate that the protein of the red blood cell in circulation is involved in a slower cycle of synthesis and destruction than the other proteins of the body. By administering[182] isotopic nitrogen in amino acids to actively immune rats and rabbits, antibody like other serum and body proteins was found to participate in metabolic reactions involving the uptake of dietary nitrogen. The rate of replacement of marked nitrogen by ordinary nitrogen was followed. This indicated the half life of the antibody molecule to be about two weeks, approximately the same as the average serum protein. In a rabbit made passively immune to an antigen by injection of antibody,[93] the absence of uptake of dietary isotopic nitrogen by the passive antibodies is in marked contrast to the appearance of tagged nitrogen in the active antibodies. Shemin and Rittenberg[186] reported that half of the nitrogen in liver proteins is replaced by nitrogen from other sources in seven days. Apparently the most active pro-

teins take up the tagged nitrogen first, then gradually let it go to other proteins until eventually there is an equilibrium of all the protein of the body. Muscle apparently is composed of heterogenous proteins, some reacting slowly with dietary nitrogen and others reacting very rapidly.

Burroughs and associates[26] felt that the discrepancy between the two views, that of Folin and that of Schoenheimer may not be so great if one considers the reactivity of various proteins from a quantitative rather than a qualitative viewpoint. While all organ proteins may be involved, they may react at different rates. Borsook and Dubonoff[21] suggested that the labile or reserve protein may be distinguished not primarily by its difference in composition, but rather by its location. Some organs, the liver,[86] intestine, and kidney,[5] change in size and protein content quickly with fasting and with changes in level of body protein. The labile protein may therefore arise in the course of a fast at first from the substance of the more labile organs.

Causes of Protein Deficiency in Surgical Patients.—

Starvation: Probably the most common cause of protein deficiency in surgical patients is simple starvation. Often this is due to a disease process that prevents the oral ingestion of food. Carcinoma about the oral cavity, esophageal lesions, both neoplastic and inflammatory, and obstruction to the gastric outlet, due either to carcinoma or benign stricture, are among the common offenders. All too frequently, however, because a disease process has precluded the use of solid food, the patient or his advisors have been at fault by the injudicious choice of a liquid diet. Varco[204] has very ably shown what can be accomplished with liquid diets containing large quantities of protein.

Himsworth,[97] Cuthbertson,[48] Elman,[60] and others[146] have pointed out that protein starvation leads to anorexia and asthenia, and thus a vicious cycle may well be established. With resumption of positive nitrogen balance, either by oral or parenteral protein feeding, a return of appetite and a feeling of well-being have been noted time and again by the author.

Altered absorption: Altered absorption of nutritiously adequate protein may be equally at fault in producing a picture of malnutrition and protein depletion. Inadequate absorption often will occur in diarrhea, ulcerative colitis, gastrojejunal colic fistula, and in fistulas of the small intestine. Increased oral intake of protein in this group often will pyramid the loss and recourse must be had to parenteral administration of carbohydrate and protein to replace the marked losses.

Changes in the gastrointestinal mucosa after starvation have been noted by Jackson.[107] Sun,[196] in a histologic study of the small intestinal mucosa after starvation, noted atrophy and sloughing of the tips of the mucosal villi. Most noticeable changes were in the duodenum and upper jejunum. Regeneration of the villi could be demonstrated ten hours after refeeding. If the villus did not regenerate, the animal would not eat and death ensued. Laycock,[119] writing of mass starvation in China, noted marked loss of appetite with diarrhea and a tendency to pass food unaltered in the stool. Cori and Cori[39] found glucose and fructose to be absorbed more slowly in rats after a forty-eight hour fast

than after a twenty-four hour fast. At a meeting of the Royal Society of Medicine in 1945, Magee[131] stated that, in the terminal stages of starvation in man a copious and persistent diarrhea with dehydration occurs. The onset of these symptoms invariably presaged a fatal end in spite of treatment. He felt that there is a progressive decline in efficiency of absorption as the process of fasting is increased. At the same meeting, Cuthbertson[131] stated that there is reason to believe that in starvation the alimentary enzymes may share in the general protein depletion and that the power to digest will therefore become affected. In contrast to the impression that there might be real interference with intestinal absorption in extreme starvation, it was the impression of Vaughan,[205] writing of her experience in the treatment of starvation and malnutrition at Belsen, that best results were obtained using large doses of skim milk orally. Similarly Berger and associates[15] after the liberation of Holland noted that protein digests given orally caused no diarrhea but best results in rehabilitation obtained from a high caloric, high protein (300 Gm.), bland diet given orally.

Altered protein synthesis: In the presence of hepatic disease, protein synthesis may be impaired. This is especially true in regard to albumin formation, reversal of the albumin globulin ratio being a common finding in hepatitis and in portal cirrhosis.[140] In addition, there may be large losses of protein in ascitic fluid. Davis and Blalock[54] returned ascitic fluid intravenously to patients in order to replace protein losses. Davis and Getzoff[55] proposed a new classification of hypoproteinemias, a prehepatic state where there is insufficient intake or poor absorption, a hepatic state where hypoproteinemia is due to decreased hepatic synthesis of protein, and a posthepatic state due to excess protein losses. Barnett and associates[11] reported a case of cirrhosis of the liver with a daily loss of 10 Gm. of protein into ascitic fluid over a seven-month period without any lowering of plasma proteins. Madden and associates[125] found that sterile abscesses produced by turpentine in hypoproteinemic dogs have a retarding effect on protein synthesis.

Excessive protein loss: Serious loss of protein may occur in nephritis where large amounts of albumin leave the circulation, producing, if severe enough, a marked hypoproteinemia. Local losses of protein from burns, blood and plasma loss from open wounds, internal bleeding, and suppuration such as empyema or peritonitis, may be of major magnitude and constitute a real drain on a patient's protein stores.

After trauma, mainly fractures, Cuthbertson[43-46] first pointed out that there is a marked increased urinary nitrogen excretion. Disuse atrophy, although it produced an undoubted but small loss of nitrogen, could not wholly account for these changes, as the loss of substance was not wholly confined to the area of trauma. This traumatic catabolism in man reached its maximum toward the end of the first week after injury and then slowly declined. With severe injuries, the ingestion of a diet rich in protein and in calories did not maintain nitrogen equilibrium at the height of the catabolic process, although it did decrease the extent of the nitrogen losses. After trauma there appears

to be a general increase of catabolism of protein in particular to meet the enhanced metabolism of the repair process.[47]

Lucido[122] reported increased urinary nitrogen excretion after burns. Cope and co-workers,[38] studying the causes of increased urinary nitrogen excretion after burns, found it was not associated with an increased potassium excretion and concluded that the excess nitrogen excreted did not come from cellular breakdown. They found the loss of nitrogen in the urine to be no greater in the severely burned than in the mildly burned. Croft and Peters[41] reported the urinary nitrogen loss after burns to be substantially reduced by inclusion of 1 per cent methionine in the diet, supplying confirmatory evidence to an earlier suggestion by Cuthbertson[45] that the increased urinary catabolism of protein after trauma was in response to a demand by the body for certain key amino acids for repair purposes, and so renders the healing process independent of dietary nitrogen. Brunschwig and associates[24] found that postoperative nitrogen loss bore no relation to the type of disease but rather was related only to the length of time the patient was deprived of food. Similarly Co Tui and associates[40, 148] felt that the principal cause of nitrogen loss in postoperative patients is starvation. Using a high nitrogen intake of protein digest given by indwelling intestinal tube they reported positive nitrogen balance can be obtained during the postoperative period. Rasmussen and associates[163] reported that by preoperative ingestion of considerable amounts of protein in patients with gastric cancer, serious degrees of hypoproteinemia can be prevented during the postoperative period of negative nitrogen balance.

Howard and associates[102] have reported augmented urinary nitrogen losses after simple fractures reaching a peak in 5.6 days and lasting up to 35 days. Peters[155] and Browne and co-workers[23] felt that a healthy man after injury or an acute infection suffers protein depletion which cannot be prevented. On the other hand, a malnourished and protein depleted individual can summon certain conservative processes that permit him to utilize protein for reconstruction of tissues.

Effects of Protein Deficiency in Surgical Patients.—

Hypoproteinemia: In the protein-deficient animal and in man this deficiency is mirrored in the blood proteins by a fall in the albumin fraction. This was well demonstrated by Weech[211] and has been confirmed by other investigators.[136, 177, 185, 200, 224] Sachar and associates[177] felt that hypoalbuminemia can be used as a quantitative measure of tissue protein depletion, postulating that for every gram of change in total serum albumin, there has been a concomitant change in the same direction of 30 Gm. of tissue protein. Madden and Whipple[128] have shown that, while the reserve stores of protein exist, a hypoproteinemic dog will produce plasma protein on a protein-free diet. Weech[211] found that on refeeding a protein deficient dog there was a slow return of plasma proteins to normal, suggesting that replenishment of the organ responsible for formation of albumin must take place before a rise of circulating plasma albumin occurs. This mechanism is apparently at play with intravenous plasma infusions also, for the rise of plasma proteins following such multiple

transfusions is very gradual and slow.[185, 213] In contrast to the fall in the albumin fraction, the serum globulins remain relatively unchanged in protein depletion.[211] Zeldis and associates[224] felt the serum globulins enjoy prior demands on the total available pool of body proteins under such emergency conditions.

Blood volume: Single or even multiple determinations of plasma protein levels may be misleading without data on total plasma and blood volume.[2] That there is a fall in blood volume with protein depletion was first pointed out by Chang,[34] who felt that the plasma proteins had a regulatory effect on blood volume. Melnick and Cowgill[135] similarly felt that the plasma proteins had a regulatory effect on the plasma volume, but only in so far as the red blood cell volume remained constant. Others[2, 123, 155, 185, 211, 217] have pointed out the existence of a contracted plasma volume in starvation and deficiency states. Abbott and associates,[1] on the other hand, have demonstrated a rise in plasma volume in the postburn shock phase that persisted from forty to ninety days. This however, is not comparable to the starvation state mentioned previously. There appears to be a reciprocal arrangement between red cell volume and plasma volume for increases in red cell mass will tend to decrease the plasma volume to keep the total blood volume relatively constant.[17, 133] In anemias, on the other hand, there may be a real as well as an apparent increase in plasma volume.[1]

Edema: Starling[192] first stressed the significance of the osmotic pressure of the plasma proteins in drawing tissue fluid into the capillaries. Present-day theories of edema formation are still explained on the basis of his theory. The major osmotic effect of the plasma proteins[76, 77] was found to reside with the albumin fraction, which, because of its smaller molecular weight, is four times as active osmotically as the globulin fraction. Moore and Van Slyke[145] postulated a critical level of total protein of 5.5 Gm. per cent, or of albumin of 2.5 Gm. per cent or a plasma specific gravity of 1.023, below which edema will occur. By varying the level of sodium chloride intake, exception to the rule occurred. Weech and associates[214] similarly showed hypoproteinemia to be associated with edema. However, they noted that a lower level of plasma protein was necessary to produce edema after plasmaphoresis than after nutritional deficiency. Clinically the effect of large salt and fluid intake as well as hypoproteinemia in producing postoperative edema was first stressed by Jones and Eaton.[108] Also they postulated that edema may be a cause of stomal obstruction in gastroenterostomy during the early postoperative phase. Ravdin[160] later pointed out the same condition and in addition felt that hypoproteinemia reduced the gastric emptying time probably because of edema of the gut wall.[134] This later finding could not be confirmed by Beams and associates,[13] who could not demonstrate any roentgenologic change in gastric motility with edema.

Liver function: In 1914, Opie and Alford,[150, 151] studying the effect of chloroform on the liver, noted that the incidence of hepatic necrosis could be reduced after a high carbohydrate diet while a high fat diet materially increased the susceptibility of the animal to develop liver necrosis. Later Davis and associates[56, 57] noted regeneration of liver tissue on a carbohydrate diet alone. Also

they observed that after chloroform anesthesia, when sugar was given, there was much less urinary nitrogen loss than when sugar was witheld. They postulated that the beneficial effect observed from sugar was due to its "protein sparing" effect. A similar effect was reported in 1936 by Daft and co-workers.[52]

In 1939 Goldschmidt, Vars, and Ravdin,[75] working with rats, demonstrated that the major protection afforded the liver to injury by chloroform was related to its protein content. They demonstrated a progressive increase of liver necrosis after chloroform anesthesia as the liver fat content increased. A high concentration of hepatic glycogen per se failed to confer any discernible protection. The liver damage increased with the lipid content independent of the glycogen content. Whatever benefit derived from glycogen was obtained by virtue of its replacing fat.[160] Protein, on the other hand, produced real protection. A high protein intake prior to chloroform anesthesia markedly reduced the incidence of liver necrosis even in those livers with a high lipid content. The injurious effect of fasting was believed to be due to its depletion of the protein stores.

Miller and associates[142, 143] demonstrated in protein depleted dogs that a single protein feeding by mouth, plasma protein intravenously or methionine and cystine may be the effective agent in this action. Brunschwig and associates[25] and others[96, 201] have reached similar conclusions. Harrison and Long[86] have shown in rats that the liver weight rapidly decreases during short periods of fasting, with the major loss being protein. Casein and lactalbumin feedings were effective in replacing this loss. However, from the time necessary to do this they felt that liver protein was not restored to its original level until after the lost body protein had been replaced. Tsan Wen Li[202, 203] stressed the effect of cholesterol which uniformly caused a higher total liver lipid content than ordinary fat. This effect could not be prevented entirely by high protein intake.

Resistance to infection and trauma: In Madden and Whipple's[128] experiments of producing protein depletion it was early appreciated that hypoproteinemic dogs were much less resistant to infection and to toxic agents. Sako[178] working with white rats concluded that animals on a high protein diet were more resistant to pneumococcus infection than a control group of animals; whereas animals on a lower protein diet were less resistant to the same organism. Further evidence of malnutrition reducing resistance to infection can be noted from the increased incidence of active tuberculosis in European countries after World War I and again at the present time. Cannon and his co-workers in a series of papers[29-32] stressed the importance of good protein reserves for formation of globulin and antibodies. In hypoproteinemic rabbits, he demonstrated a deficiency of antibodies.[31] That dietary nitrogen participates in formation of antibodies has been shown with isotopic nitrogen by Schoenheimer and associates.[182] In the foregoing discussion, it was shown there is good evidence to believe that protein depletion is associated with a decreased blood volume. In hypoproteinemic dogs, Ravdin and associates[161] demonstrated a 67 per cent increase in susceptibility to hemorrhagic shock.

Wound healing: In 1919 Clark,[36] working on dogs, showed that the lag phase in wound healing was markedly shortened with a high protein diet.

Harvey and Howes,[89] working on stomach wounds in rats, found no change in the lag period, but did note that once growth had started its rate was noticeably increased by a high protein diet. Thompson and associates,[198, 199] Hartzell and associates[87] and A. O. Whipple[216] wrote of the importance of adequate protein stores for wound healing, and of the high incidence of wound disruption in hypoproteinemic patients. Thompson and co-workers[199] noted an accelerated decline in tensile strength of catgut in hypoproteinemic dogs and recommended that silk be used in its place. A decreased formation of callus in hypoproteinemic dogs was reported by Rhoads and Kasinskas.[165]

In summary, it can be said that the effects of protein deprivation are legion. In the past, related clinical conditions such as pulmonary edema, failure of wounds and anastomoses to heal, sepsis, hepatorenal syndrome, and a poor response to operative trauma and anesthesia may have been dismissed as unavoidable complications. Such conditions, however, are not distantly related to the effects of protein deprivation. It has been only in recent years, when surgeons have concerned themselves with phases of the patient's care in addition to good operative technique, that operative mortalities have declined. It is not the operation per se, but one of its complications which prolongs convalescence and often ends fatally. In uncomplicated major operative cases the patients are ready for dismissal from the hospital in four to five days. A smooth uncomplicated convalescence should be the goal toward which the surgeon embarks on each case. In attaining that goal, attention to many details is necessary, one of which should be an effort to correct the protein-deficient state in poorly nourished patients.

THE RELATIONSHIP OF HEMOGLOBIN METABOLISM TO BODY PROTEIN METABOLISM

In normal man there is a continuous destruction of erythrocytes and a continuous replenishment of new red blood cells from the hematopoietic tissue.[210] An equilibrium between these processes in health maintains the hemoglobin level at around 15 Gm. per cent. Many studies of the average life of the red blood cell have been made. By selective agglutination of donor red blood cells in a recipient's circulation and from the rate of their disappearance, Ashby[9] and others[50, 105, 221] concluded that the survival time of transfused erythrocytes may vary from 50 to 120 days. From a study of bilirubin and urobilinogen excretion, Hawkins and Whipple[91] and others[208] found similar results. Shemin and Rittenberg[187] fed glycine containing isotopic nitrogen, thus incorporating it into the heme fraction of hemoglobin. They concluded that the average life of the red blood cell was 125 days. Other studies[82] using radioactive iron incorporated into the red blood cell were nonconclusive in determining the life of the erythrocyte, for no change in the amount of radioactive iron in the circulating red blood cells could be noted after 120 days. It was felt that the iron liberated by the breakdown of red blood cells was promptly reutilized in the formation of new red blood cells. Hence, no change could be detected in the circulating level of radioactive iron.

The actual site of destruction of red blood cells is not clear. Three possibilities exist, hemolysis, phagocytosis, and fragmentation. Rous and Robert-

son[170, 175, 176] state that phagocytosis of red blood cells while frequent in the dog, rat, and guinea pig is slight in man, rhesus monkey, and rabbit. They find no support for the thesis of hemolytic destruction of erythrocytes and feel that the principal means of red blood cell destruction is by fragmentation of erythrocytes in the circulation due to aging of the cells and to the stress and strain they are subjected to in their passage through the blood vessels and capillaries. Fragments of various portions of red blood cells can be observed in the circulation and these in turn are removed by the reticuloendothelial system. In summarizing the prevailing views on the fate of the liberated hemoglobin, Rous in 1923[175] stated that the hemoglobin was broken up into globin, the fate of which was unknown, into bilirubin, which was excreted in the bile; and into an iron-containing substance which was retained by the body and possibly utilized. Isaacs[105] in 1937 stated that the concepts of red blood cell destruction were unchanged since the papers of Rous.

Apparently the hemoglobin[181] of the intact red blood cell does not participate in the rapid interchange of amide groups as do the proteins of the remainder of the body. It seems to have a separate and slower cycle of synthesis and destruction than the other body proteins. Hahn and associates[81] and Whipple[218] and Shemin and Rittenberg[187] have shown that the hemoglobin of the red blood cell apparently remains intact as long as the cell exists, and similarly its component iron is not subject to physiochemical change for the life span of the erythrocyte. When the red blood cell is destroyed, the iron is retained by the body and reutilized for new hemoglobin formation,[91] possibly more promptly than iron in storage[42, 82] and certainly in preference to dietary iron.[80]

Itami in 1908[106] postulated that experimental plethora may have a depressing effect on hematopoiesis. Boycott and Douglas[22] in 1910 found that just as anemia can be a stimulus to red blood cell formation, excess circulating red blood cells can be a stimulus to red blood cell destruction in an effort by the body to adjust to a normal status. This problem was again studied by Robertson and Rous[170] in 1917, who gave daily transfusions of whole blood to rabbits. They were not able to produce plethora uniformly, but in some animals hemoglobin levels up to 150 per cent of normal occurred. Concomitant with the production of plethora a decrease of reticulocytes in the circulating blood occurred and often they completely disappeared, to reappear again only when the hemoglobin returned to normal levels. Bone marrow biopsies similarly showed a marked decrease in the number of reticulocytes.

In 1936 Melnick and associates[137] stated that the slow continuous breakdown of injected red blood cells after plasmaphoresis experiments liberated globin which is completely metabolized similar to dietary protein, and in so doing it erased the amino acid deficiency of gliadin.

In a series of papers recently published by Strumia and associates[193, 194] the claim was made that globin prepared by extracorporeal hemolysis of erythrocytes can be given parenterally with good utilization. They felt that it could be

converted to plasma protein, citing a 90 Gm. increase of plasma protein after administering 260 Gm. of globin, or a three to one conversion ratio.

In 1935 Pommerenke and associates,[159] working in Whipple's laboratory, reported that hemoglobin and globin could not be utilized by the body. They administered dog hemoglobin intravenously to dogs and noted increased urinary nitrogen excretion equivalent to the amount of hemoglobin nitrogen administered. Similarly Madden and co-workers[127] stated that laked red blood cells afforded little if any material for plasma protein formation when given intravenously. They found no increased plasma protein formation when red blood cells were given intravenously in addition to a basal diet. In later papers[126, 141, 168, 169, 218, 219] from the same laboratory, however, it is reported that hemoglobin and hemoglobin digests given intravenously and parenterally will support nitrogen balance and produce new plasma protein.

Whipple writing in 1942[218] stated:

> Hemoglobin in its production may draw on the plasma protein, but hemoglobin stands apart in the protein economy and does not contribute freely to the protein pool. On the other hand, the body guards jealously the fabrication of hemoglobin and given a real need for both plasma protein and hemoglobin the protein flow favors hemoglobin which under these circumstances is always produced in more abundance than plasma proteins.

In 1944 Whipple and Madden[219] wrote:

> Hemoglobin cannot be contributed to the body protein pool except when the red blood cell is broken up. Hemoglobin is then saved, supplemented, and recast into new protein depending upon the body needs, and much of the rescued hemoglobin or globin may contribute to the building of plasma protein.

In 1933 Daft[51, 52] demonstrated that under conditions of protein starvation the anemic dog can fabricate new hemoglobin from its own body proteins. This is associated with a decrease urinary nitrogen excretion over similar nonanemic periods. Later Hahn and Whipple[85] pointed out that limitation of protein intake eventually will limit the formation of globin and thus cut down the formation of hemoglobin. Since the body can manufacture unlimited quantities of porphyrin pigment, the limiting factors in hemoglobin formation are iron and protein. Similarly Orten and Orten[152] and others [215] showed that a low protein diet produced anemia, whereas an isocaloric diet high in protein resulted in normal hemoglobin levels. They felt that protein building blocks are not available for hemoglobin synthesis under conditions of protein starvation. Taylor and Lytle[197] found that in patients, both hypoproteinemic and anemic, infusions of red blood cells resulted in a definite rise of plasma proteins. This they attributed to a sparing effect on protein which otherwise would have been used for hemoglobin formation. In 1946 Robscheit-Robbins and associates[169] stressed the point that in doubly depleted dogs (hypoproteinemic and anemic) hemoglobin is always produced more abundantly than and often at the expense of plasma proteins.

From the foregoing discussion it may be surmised that hemoglobin formation constitutes a real drain on the protein stores of the body, and will con-

tinue even in the fasting state and at the expense of plasma proteins. Also as red blood cells are being destroyed, the proteins of the liberated hemoglobin are made available to the general body pool of proteins for whatever use is most urgent at the moment. From a nutritional viewpoint the administration of whole blood transfusions offers several avenues of benefit to the over-all protein economy of the body. First, protein from the body stores which would have, by priority, been used for building hemoglobin may now become available for other purposes. Second, the plasma proteins contained in the whole blood are available for use in the body economy and, third, as the total circulating hemoglobin or red cell mass is increased, more red blood cells will be destroyed daily liberating their contained hemoglobin, the protein of which also becomes available for general body utilization.

CONSIDERATIONS IN PROTEIN REPLACEMENT THERAPY AND REAFFIRMATION OF THE PROBLEM

The average adult in health when fed adequate quantities of carbohydrate and on a protein-free diet will excrete from 4 to 6 Gm. of nitrogen per day in the urine.[59, 113] This amount is equivalent to 25 to 37.5 Gm. of protein. In addition, if oral feedings are being taken, up to 10 per cent of the ingested nitrogen may normally be excreted in the stools without diarrhea.[144] Chittenden[35] proposed 0.65 Gm. of protein per kilogram body weight as an adequate protein intake for a healthy man. To create an adequate margin of safety most recommendations are placed on a higher level of protein intake. The League of Nations[58] recommendation was set at 1 Gm. of protein per kilogram of body weight per day. A similar figure was reported by Cuthbertson[48] and by the National Research Council[149] with the added recommendation that one-third to one-half of the protein intake be of animal origin and the remainder of vegetable origin. This is in recognition of the fact that proteins of animal origin are more complete in essential amino acids. For replacement therapy when the protein stores of the body are depleted, amounts of protein in the order of magnitude of two to four times this figure may be beneficial[61, 204] and utilized.

The sparing effect of carbohydrate on the body's consumption of its own protein or on ingested protein has been attested to by many authors. Landergen[114] in 1903 showed that urinary nitrogen excretion is markedly reduced on a rich carbohydrate diet. Similarly Cathart[33] showed that urinary nitrogen excretion is less when carbohydrate is consumed than under conditions of total fasting. Shaffer and Coleman[184] reported a decreased nitrogen loss with typhoid fever when a high carbohydrate intake is assured. Writing on the protein sparing action of carbohydrate in 1919, Davis, Hall and Whipple[57] postulated two possible mechanisms for its action: one by conserving the end products of protein catabolism and the other by sparing the autolysis of protein. They felt that both actions may occur. When sufficient carbohydrate is available for energy requirements, protein catabolism is reduced to a minimum. In the absence of sufficient carbohydrate, protein can be used for energy purposes and 58 per cent of it may be converted to carbohydrate, the so-called D/N

ratio.[166] More recently others[7, 49, 104, 117, 162] have attested to the protein sparing action of carbohydrate, and to the attainment of increased nitrogen retention when protein is given in conjunction with a high sugar intake, preferably at the same time. Daft and associates[53] suggested that possibly protein intoxication can occur. They noted excessive urinary nitrogen excretion when large doses of protein alone were administered. It was possible to prevent this excess loss of nitrogen by feeding adequate carbohydrate and fat with the protein. Elman and co-workers[63] recently stated that nitrogen retention can occur with a sufficiently high nitrogen intake and an inadequate caloric intake, with the caloric deficit being made up by body fat. This is in contradistinction to reports by Landergen[114] and Cathart,[33] early in this century, who noted much poorer nitrogen retention when fat was substituted for carbohydrate in the diet.

In 1935 Kochakion and Murlin[112] demonstrated that male sex hormones, extracted from urine, constantly led to nitrogen retention when administered to castrated dogs. Kenyon and associates[109, 110] noted that testosterone led to increased nitrogen retention and decreased urinary nitrogen excretion in normal men as well as in eunuchoids, although to a lesser extent in the former. One normal young woman responded in a similar fashion. They feel the effect is related to the stimulus to growth associated with puberty. Similar results are reported by Abels and co-workers.[4] Albright[8] has postulated that the adrenal gland produces an "N" or protein anabolic hormone and an "S" or sugar or antianabolic hormone and that normally these are balanced. After injury there may be a decreased excretion of "N" and an increased excretion of "S" hormone producing the increased catabolism of protein described earlier.

The exact amount of protein replacement necessary, prior to embarking on a major operative procedure, cannot be stated categorically. Studley[195] in 1936 reported that the percentage of weight loss by the patient was a good indicator of the surgical risk of that patient. He reported on forty-seven patients with complicated peptic ulcer who were operated upon. In twenty-nine patients who had lost less than 20 per cent of their body weight there was one death, a mortality of 3 per cent, whereas in eighteen patients who had lost over 20 per cent of their body weight there were six deaths, a mortality of 33 per cent. Varco[204] on similar considerations postulated progressively increasing periods of preoperative dietary preparation, the length of preparation being in direct proportion to the weight loss of the patient. In extreme cases, periods of preoperative preparation up to one month are suggested.

However, if the weight loss has been chiefly from the fatty depots no harm will result. In evaluating weight loss one should consider the past dietary history as well as the status of the patient's nitrogen balance. Similarly, the state of hydration can effect weight figures by as much as 10 per cent. Complete replacement of the total protein loss is often impossible and not very practical. Certainly, however, positive nitrogen balance should be established, hypoproteinemia and hemoglobin deficits corrected, and the contracted blood volume that may accompany malnutrition restored to normal by the most propitious means. With a cooperative patient, in whom no obstruction to the

esophagus, stomach, or bowel exists, or in whom no avenues of increased food loss such as ulcerative colitis, external intestinal or gastrojejunocolic fistula exists, oral feeding of a high protein, high carbohydrate, and low fat diet is undoubtedly the best avenue of supplying vitally needed protein. For the group of patients, as just mentioned, in whom the oral route is not available, parenteral feeding is necessary.

It is possible to supply parenterally all the essential food elements: water, minerals, vitamins, carbohydrates, and protein. Possibly fat should be included in this group[28] and its parenteral administration has been accomplished,[37, 100] but as yet this method has not reached the stage of clinical trial. Gastrostomy or jejunostomy performed for feeding purposes and preliminary to a major surgical procedure may have rare instances of usefulness, but this should not be necessary often. It subjects a patient to the risk and discomfort of an additional operation, with its subsequent period of increased protein catabolism. In neoplastic diseases of the intestinal tract it is not an uncommon occurrence to return to the peritoneal cavity three to four weeks after having done a jejunostomy for feeding purposes to find what was previously a well-localized carcinoma has spread beyond its original site. The best time to cure cancer is at the initial operation.

In the following sections it will be shown that the positive nitrogen balance can be achieved by parenteral administration of plasma proteins, whole blood, and protein digests. Also it will be shown that these poor-risk patients who cannot be prepared by oral means can be prepared parenterally and will withstand operations of major proportions with risks not greater than similar uncomplicated cases.

CONSIDERATIONS OF PARENTERAL THERAPY

The history of parenteral therapy dates from 1628 when William Harvey[90] discovered the circulation. Dr. Wren (later Sir Christopher)[111] in 1657 first injected medicinals into the veins of animals and reported his findings at one of the early meetings of the Royal Society which had been started in London in 1661. To Richard Lower, also a member of the Royal Society, and stimulated by the work of Harvey and Wren, belongs the credit for giving the first blood transfusion from dog to dog in February, 1666. One year later Jean Denys of Montpellier, and physician to Louis XIV, pursued similar experiments and on June 15, 1667, he transfused into a boy of 15 years, 9 ounces of lamb's blood with no untoward effect. As might have been expected, when these attempts of transfusing animal blood into man continued, fatalities occurred and in 1670 a writ appeared specifically prohibiting the operation of transfusion in France. Similarly in 1678 an edict of Parliament appeared specifically prohibiting the operation of transfusion in England. On Dec. 22, 1818, James Blundell[19] gave the first blood transfusion from man to man. Out of ten transfusions given by Blundell, four were successful. Before blood transfusions could be rendered safe and be performed with relative ease and dispatch, it remained for the work of Landsteiner[116] to demonstrate the four blood groups in man,

and for Lewisohn[120, 121] to offer an efficient, practical means of avoiding coagulation of blood by the use of sodium citrate solution.

The first intravenous injection of saline solution was made by Thomas Latta[118] in 1831 for treatment of the dehydration of cholera. To Claude Bernard[16] in 1843 belongs credit for first injecting carbohydrate intravenously. He showed that sucrose, when injected intravenously, soon appeared in the urine, but, if it had been previously acted upon by gastric juice and converted to glucose, it was apparently utilized. Woodyatt and associates[223] first postulated that intravenous nutrition in man might be accomplished by intravenous injection of glucose when he showed that normal man can utilize from 0.8 to 0.9 Gm. of glucose per kilogram per hour. If this rate were exceeded, glycosuria and diuresis would occur. He also warned that death could occur from dehydration from the diuretic effect of extremely large doses of hypertonic intravenous glucose given too rapidly over prolonged periods.

In 1912 Austin and Eisenbrey[10] expressed the belief that dogs could utilize dog and horse serum administered intravenously as a source of tissue nitrogen. They determined the urinary nitrogen excretion on a nitrogen-free diet, following which they administered dog and horse serum intravenously to dogs. This was not associated with any increased urinary nitrogen excretion over the control period. Although their figures do not show positive nitrogen balance, they did find that the protein so administered was retained and used by the body. From the laboratory of Whipple and associates[99] in 1934 and in numerous subsequent reports,[128, 159] it was demonstrated that positive nitrogen balance in animals and man[113, 207] could be obtained using homologous plasma intravenously as the sole source of protein intake.

Plasma protein given intravenously soon disappears from the circulation, apparently going into the general body protein stores. Shearburn[185] using blood volume studies, found an initial rise of circulating plasma protein following massive plasma transfusion. In three days he noted that all the injected plasma proteins had apparently left the circulation. Using protein tagged with radioactive sulfur, Fine and Seligman[66] observed the rate of disappearance of tagged plasma protein from the circulation of normal dogs. At five hours, 90 per cent of the protein remained in the circulation; at fifteen hours, 70 per cent was present; by forty-eight hours, 55 per cent of the tagged plasma protein had left the circulation. They observed similar disappearance curves of plasma protein in shocked animals. Fink and associates[67] in a similar study, but using heavy nitrogen in the lysine fraction of the plasma proteins, reported the same findings. These studies confirm the clinical findings that hypoproteinemia is not readily corrected by plasma transfusions. Apparently depleted protein stores must first be restored or at least must concomitantly be restored as was first suggested by Weech[211] in the case of oral feedings. Sachar and co-workers[177] have computed that plasma proteins are restored in a ratio of one to thirty with body protein stores.

In 1905, Abderholden and Rona[3] demonstrated that nitrogen equilibrium in a dog could be maintained by feeding a pancreatic digestion product of

casein containing amino cleavage products equal to 2 Gm. of nitrogen. When the same protein was hydrolysed with acid and an equivalent amount of nitrogen was administered, negative nitrogen balance resulted. The nitrogen loss was equal to that on a nitrogen-free diet. Henriques[94] showed that in the absence of the single amino acid, tryptophane, nitrogen equilibrium cannot be attained. Henriques and Anderson,[95] in 1913, first demonstrated that nitrogen equilibrium could be obtained in the goat by intravenous injection of amino acids (meat digested with trypsin and erypsin plus tryptophane) as the sole source of nitrogen for eighteen days. It is of interest that they chose the goat as their experimental animal so that they could utilize its horns for fixing their intravenous apparatus which they maintained in the jugular vein for long periods. Through the work of Osborne and Mendel[153, 154] and later Rose and associates[171, 172] the nutritutive significance of amino acids for growth was established. Ten amino acids: lysine, leucine, isoleucine, threonine, methionine, phenylalanine, tryptophane, valine, histidine, and arginine, were found to be essential to the body for growth. They cannot be synthesized or substituted for by the body and must be supplied in the food. Burroughs and co-workers[27] postulated a difference between growth where total protein synthesis must occur, and for maintenance of nitrogen equilibrium in an adult where only particular requirements must be met. For such a state lysine, histidine, and arginine may possibly be dispensed with. Elman and Weiner,[64] in 1939, first reported the use of an acid hydrolysate of casein with added tryptophane and cystine for intravenous alimentation and reported positive nitrogen balance with its use. The first clinical use of an enzymatic hydrolysate of casein in which all the essential amino acids are present was reported by Shohl, Butler, and Blackfan[188] and Farr and MacFadyen.[65] Shohl and Blackfan,[189] in 1940, reported a crystalline amino acid solution to be equally effective as an enzymatic hydrolysate of casein in achieving positive nitrogen balance when given intravenously to children. However, their observation periods were only for twelve to twenty-four hours.

In 1940, it was shown that growth of rats was the same when fed casein, or the casein enzymatic digest, amigen, as the sole source of protein.[147] Later, Horwitz and associates[101] claimed growth in rats using amigen as the sole source of protein, subcutaneously. Shohl[190] found nitrogen retention to be equally good when amigen was given either orally or intravenously. From his data it is noted that nitrogen retention was greater both in amount and in proportion to intake when blood transfusions were given in addition to amigen. Madden and co-workers[130] reported that a papain casein digest was found to be equally as effective in producing plasma protein when given either orally or intravenously. However, a greater urinary nitrogen excretion was noted after intravenous administration than after oral feeding of the digest. Others[193, 194] have noted a pyramiding of urinary nitrogen excretion when protein digests are given intravenously. Mixtures of the ten essential amino acids, as described by Rose, were found to rate with the best food proteins in producing new plasma protein.[124, 129] Positive nitrogen balance could be achieved equally well with either oral or intravenous administration.

The mixtures of pure amino acids could be given several times faster than the fastest tolerable rate for protein digest without producing clinical disturbance. Glutamic acid[126] was suggested as being the causative agent in producing nausea and vomiting. Hoffman and associates[98] noted nausea and vomiting occurring in human beings after amigen injection when the blood amino acid level rose above 10 mg. per cent.

EXPERIMENTAL: NITROGEN BALANCE STUDIES

Method.—In order to assay the effectiveness of a given material for parenteral feeding purposes, nitrogen balance studies were performed on selected patients using bovine plasma, human plasma, whole human blood, and casein digests* given intravenously as the sole source of nitrogen intake. These materials were tested individually and in combinations. It was felt that the ability of a nitrogenous material to sustain positive nitrogen balance when given intravenously as the sole source of nitrogen intake would constitute a critical test of that material's ability to sustain protein metabolism and to replenish depleted protein stores.

Subjects were chosen who had lost considerable weight, usually because a carcinoma of the esophagus or stomach had precluded their taking an adequate diet by mouth. All patients were afebrile and were allowed out of bed ad libitum while fluids were not running.

The selection of a proper subject for such a study requires the fulfillment of several considerations. First, the patient's disease must be such to justify and require a prolonged period of parenteral feeding. Second, the cooperation of the patient must be secured so that specimens will not be lost, will be passed on time, and will be passed into the proper receptacle. Third, there must be an adequate number of patent peripheral veins on the arms, hands, and legs, for in the course of such a study many of the vessels will become thrombosed. As the studies progressed, it was appreciated that as a rule men made better subjects for study. They had less difficulty in passing urine and feces separately, whereas even with repeated warning, women would on occasion pass urine at the time of bowel movements. During the period of study the patients were on a protein-free oral intake of sweetened fruit juice and tea. Usually 3000 c.c. of 10 per cent glucose solution, supplying 1,200 calories, was given intravenously daily along with 4.5 Gm. of sodium chloride and therapeutic doses of vitamins B, C, and K. Total urinary output was collected daily, preserved with toluene, and quantitatively analyzed for total nitrogen by the macro Kjeldahl technique,[156] urea nitrogen,[73] amino acid nitrogen,[74] ammonia,[72] creatinine,[157] and sugar.[88] Although all urine specimens were collected and analyzed daily, some of the earlier data were accumulated by periods and are so reported. After an initial test period, during which time there was no nitrogen intake, the urinary nitrogen excretion reached a basal level of around 5 Gm. per day. The test protein or protein digest solution was then given

*Two casein digests were used. One, amigen, an enzymatic hydrolysate of casein, was supplied by the Mead Johnson & Co., Evansville, Ind. The other, parenamine, an acid hydrolysate of casein fortified with tryptophane, was supplied by Fredrick Stearns & Company, Detroit, Mich.

intravenously, in addition to the dextrose solution, daily for four to six days followed by another basal period to determine any delayed nitrogen spillage, if such occured. In some cases the stools were collected by periods and preserved with glacial acetic acid. Total fecal nitrogen excretion was then determined by macro Kjeldahl technique.[156] In Tables VIII and IX, quantitative fecal urobilinogen[209] was determined. The low values of urobilinogen obtained were felt to be due to the fact that there was no oral intake of food during the time and the amount of stool passed was quite meager.

At the beginning and end of each study period, and once during a study period, hemoglobin determinations by the oxyhemoglobin method using a Leitz photoelectric colorimeter, red blood cell counts, hematocrit,[222] total and fractional plasma protein,[78] urea nitrogen,[73] plasma chloride,[220] uric acid,[73] and amino acid levels[74] were determined in the patient's blood. Total nitrogen content of donor plasma and whole blood was determined by macro Kjeldahl technique on an aliquot of each specimen. Blood volume determination, when performed, was done by the technique recommended by Gregerson,[79] using an Evelyn photoelectric colorimeter.

Results of Nitrogen Balance Studies.—From 1939 through 1941, an investigation of the possibility and potentialities of using whole bovine plasma as a blood substitute in man was carried out. These results were published in two papers, in 1940[207] and 1942.[113] It was shown that large doses of bovine plasma or serum could be given to man, but its use was attended by a large (66.6 per cent) incidence of reactions. The incidence of these reactions could be reduced, but could not be abolished by preliminary adsorption of bovine plasma with human red blood cells which partially removed a hemolysin contained in the plasma. Using such a procedure, the incidence of reactions was reduced to 24.5 per cent.

In the course of these investigations, nitrogen balance studies using bovine serum, given intravenously, as the sole source of protein intake were carried out. The results of one such study are shown in Table I and Fig. 1. The patient, O. W. (U. H. No. 702623), was a 48-year-old man with an inoperable carcinoma of the sigmoid colon. Before admission to the hospital the patient had experienced a weight loss of forty pounds, amounting to 34 per cent of his normal body weight. Beginning twelve days after an exploratory laparotomy and transverse colostomy, the patient was started on a nitrogen balance study. During the preliminary period, when there was no protein intake, the total urinary nitrogen excretion was 47.32 Gm. with an average daily nitrogen excretion of 7.88 Gm. This is a somewhat higher figure than most of our studies have shown during the basal period of protein starvation, with a caloric intake maintained at around 1,500 daily. From Jan. 9, 1941 through Jan. 13, 1941, 500 c.c. daily and a total of 2,500 c.c. of whole bovine serum, containing a total of 30.75 Gm. of nitrogen, were administrated intravenously. The remainder of the conditions were identical with the basal period. It is noted there was no increased urinary nitrogen excretion during this period, but rather a slight decrease as shown by an average daily nitrogen excretion of 6.91 Gm. as compared to 7.88 Gm. excreted during the basal period. Although positive

nitrogen balance was not achieved, nitrogen equilibrium was almost reached as compare 6.15, the average daily nitrogen intake, against 6.91, the average daily nitrogen excretion. During the subsequent period, Jan. 14, 1941 through Jan. 17, 1941, when again there was no protein intake, it is noted there was no augmented urinary nitrogen excretion over the preliminary basal period, indicating that no delayed catabolism of the ingested protein occurred. At no time was any protein noted in the urine. Also, there did not appear to be any shift in the urine urea nitrogen to total urine nitrogen ratio which might indicate an abnormal catabolism of protein. The circulating plasma proteins appear to have risen slightly from a level of 5.62 Gm. per cent at the beginning of the experiment to 6.19 Gm. per cent at the completion of the injection period. However, without blood volume determination one cannot definitely substantiate that impression. Nevertheless, from these studies it would appear that bovine plasma protein given intravenously to man, although not capable, in the amounts used, to produce positive nitrogen balance, is retained by the body for nitrogen metabolism or for replenishment of protein stores.

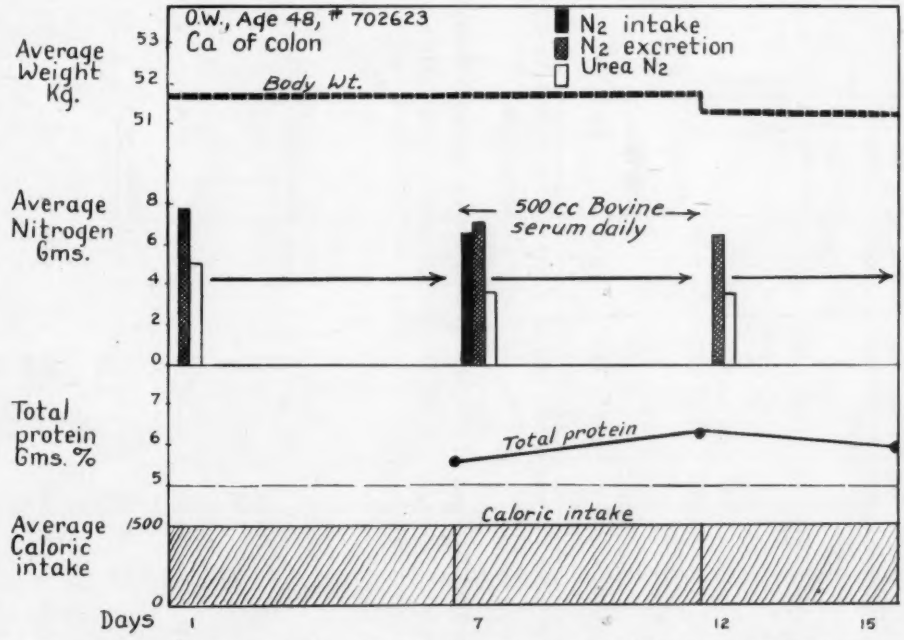

Fig. 1.—Nitrogen balance study attending intravenous administration of bovine serum.

In Table II and Fig. 2 are shown the results of a similar study of nitrogen balance attending the intravenous administration of equivalent amounts of nitrogen in the form of the casein digest, amigen, and whole human plasma. The patient, J. O. (U. H. No. 695929), a man, had a carcinoma of the hepatic flexure of the colon. He had complained of weakness, anorexia, and a weight loss of twenty-five pounds, amounting to 20 per cent of his normal body weight. He was operated upon Aug. 16, 1940, at which time exploratory laparotomy revealed the lesion to be unresectable and nothing further was done. On the

TABLE I. NITROGEN BALANCE STUDIES ATTENDING INTRAVENOUS ADMINISTRATION OF BOVINE SERUM

O. W., U. H. No. 702623, aged 48 years, carcinoma of colon

		URINE		BLOOD					
PERIOD	DATE	TOTAL N_2 (GM.)	UREA N_2 (GM.)	TOTAL PROTEIN (GM.)	N.P.N. (MG. %)	B.U.N. (MG. %)	DAILY CALORIC INTAKE	NITROGEN INTAKE AS BOVINE SERUM INTRAVENOUSLY (C.C.)	WEIGHT (KG.)
1	1/3/41 through 1/8/41	47.32	28.54	5.62	23	10.5	1500	0	51.8
	Av. daily	7.88	4.91						
2	1/9/41 through 1 13/41	34.55	17.28	6.19	23.3	15	1500	2500	51.8
								Total N 30.75 Gm.	
								Av. daily 6.15 Gm.	
	Av. daily	6.91	3.46						
3	1/14/41 through* 1/17/41	25.80	13.73	5.95	32		1500	0	51.3
	Av. daily	6.45	3.43						

*Patient developed general urticaria and edema lasting 2 days, from 1/15/41 to 1/17/41.

TABLE II. NITROGEN BALANCE ATTENDING INTRAVENOUS ADMINISTRATION OF AMIGEN AND OF HUMAN PLASMA

J. O., U. H. No. 695929, aged 51 years, carcinoma of colon

		URINE		BLOOD					
PERIOD	DATE	TOTAL N_2 (GM.)	UREA N_2 (GM.)	TOTAL PROTEIN (GM.)	N.P.N. (MG. %)	B.U.N. (MG. %)	AVERAGE DAILY CALORIC INTAKE	NITROGEN INTAKE	WEIGHT (KG.)
1	8/29/40 through 9/2/40	15.06	9.37	5.73	29.75	9.4	660	0	46.8
	Av. daily	3.01	1.87					1000 c.c. 5 % amigen I.V. daily	
2	9/3/40 through 9/8/40	51.59	34.14	5.88	27.8	17.2	1350	Total N 36.0	46.5
	Av. daily	8.59	5.83					Av. daily 6.0	
3	9/9/40 through 9/12/40	25.04	17.17	6.03	28.2	14.7	600	0	45
	Av. daily	6.26	4.29					500 c.c. whole human plasma daily IV	
4	9/13/40 through 9/17/40	21.88	13.80	6.09	26	14.7	600	Total N_2 28.0	44.2
	Av. daily	4.37	2 76					Av. daily 5.6	
5	9/18/40 through 9/22/40	16.95	9.53	6.38	30.3	11.2	1000	0	44.3
	Av. daily	3.39	1.90						

tenth postoperative day, the present study was started. During Period 1, when there was no protein intake, the urine nitrogen excretion averaged 3.01 Gm. per day. In Period 2 the patient received, in addition to the same fluids given during Period 1, 1000 c.c. of 5 per cent amigen solution containing 6 Gm. of nitrogen intravenously daily. This was associated with a prompt rise of urinary nitrogen excretion so that the patient remained in negative nitrogen balance of 2.59 Gm. of nitrogen per day. Again in Period 3, there was no nitrogen intake and the urinary nitrogen excretion declined, there being noted an average urinary nitrogen loss of 6.26 Gm. per day. This was due to an augmented urinary nitrogen spillage during the early part of the period, a delayed effect from the amigen period, while during the latter days of the period the urinary nitrogen excretion more closely approached the original

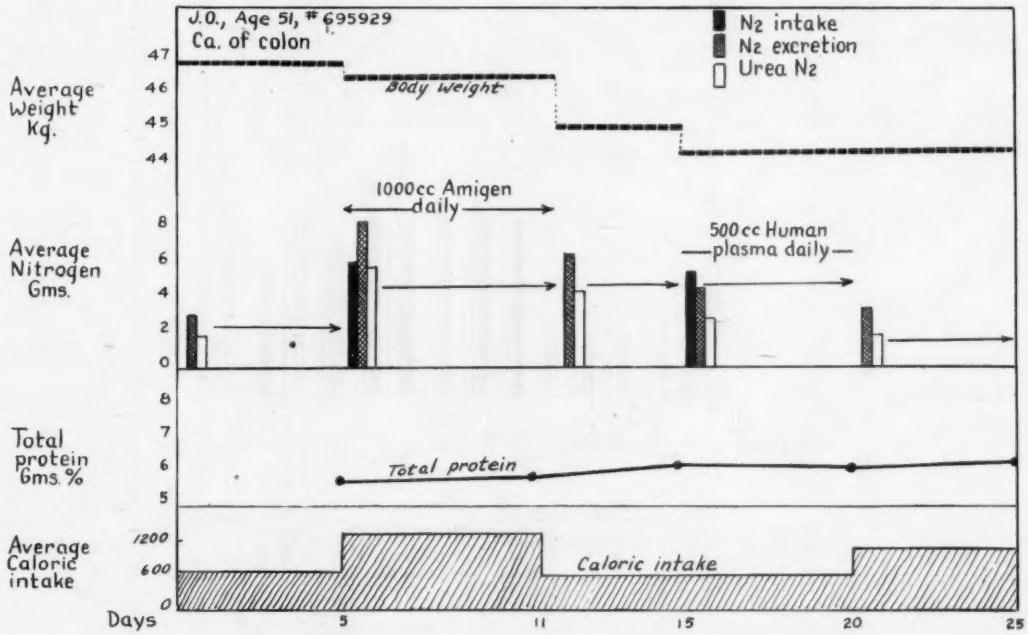

Fig. 2.—Nitrogen balance study attending the intravenous administration of amigen and whole human plasma.

basal level. During the five days of Period 4, the patient received intravenously daily as the sole protein intake 500 c.c. of human plasma, containing an equivalent amount of nitrogen, 5.6 Gm. per day as determined by Kjeldahl analysis. In contradistinction to Period 2 there was no rise of urinary nitrogen excretion noted, and definite positive nitrogen balance, a daily intake of 5.6 Gm. against a daily urinary excretion of 4.37 Gm., was obtained. In Period 5 no delayed excess nitrogen spillage over the basal period was noted, indicating that the plasma protein given was apparently retained by the body. No significant change in total circulating plasma protein was noted during the experiment. During the twenty-five day span of this study, in a patient with far advanced inoperable carcinoma of the colon, and while the metabolic requirements were met by parenteral feedings, there was a weight loss of 2.5 kg.

In Table III and Fig. 3 are recorded the results of another nitrogen balance study attending the use of intravenous amigen. This patient, C. S. (U. H. No. 698650), a 62-year-old man, had about three months earlier, a gastric resection for carcinoma of the stomach. At the time of the study he had developed almost complete obstruction at the gastrojejunal anastomosis, presumably from recurrent carcinoma. He was unable to sustain himself by oral feeding, and there had been a thirty-five pound weight loss experienced in eight months, amounting to 26 per cent loss of his normal body weight. In Period 2, when

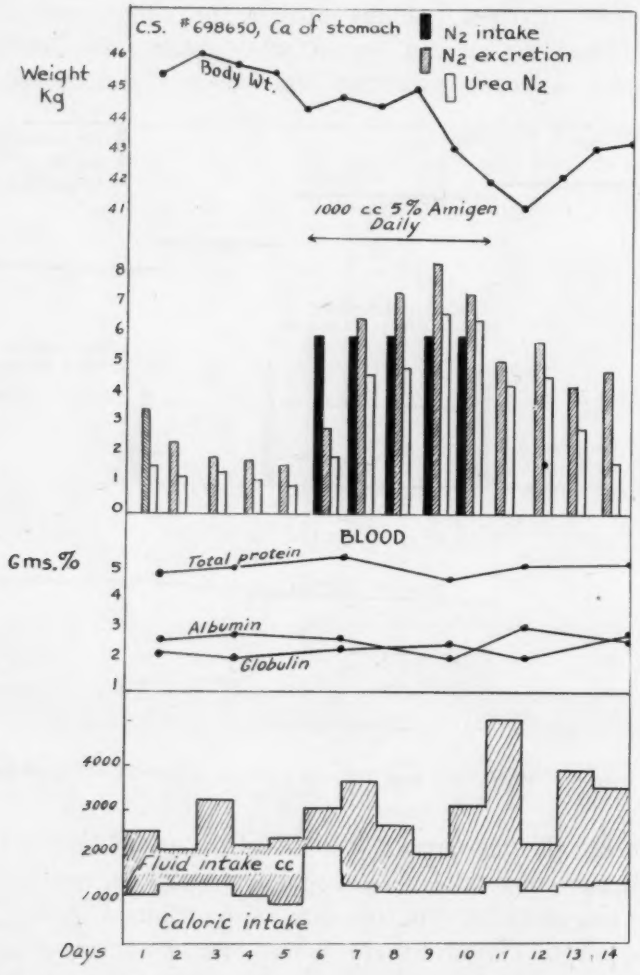

Fig. 3.—Nitrogen balance study attending the intravenous administration of amigen.

6 Gm. of nitrogen contained in 1000 c.c. of 5 per cent amigen solution was given intravenously daily as the sole source of nitrogen intake, a pyramiding of nitrogen excretion over the basal figure occurred and positive nitrogen balance could not be achieved. Again during the follow-up period (Period 3) the urinary nitrogen excretion gradually fell until it approached the basal figure. Similar results are shown in another study, on J. B., summarized in Table IV and Fig.

TABLE III. NITROGEN BALANCE STUDY ATTENDING INTRAVENOUS ADMINISTRATION OF AMIGEN

C. S., U. H. No. 698650, carcinoma of stomach

		URINE				BLOOD									
PERIOD	DATE	VOL. (C.C.)	TOTAL N_2 (GM.)	UREA N_2 (GM.)	AMINO ACID N_2 (GM.)	TOTAL PROTEIN (GM. %)	ALBUMIN (GM. %)	GLOB-ULIN (GM. %)	N.P.N. (MG. %)	B.U.N. (MG. %)	AMINO ACID (MG. %)	CAL. INTAKE	N_2 INTAKE (GM.)	WEIGHT (KG.)	FLUID INTAKE (C.C.)
1	12/18/40	1230	3.49	1.68	.096	5.0	2.77	2.23	24.3	20.2	5.3	1108	0	45.6	2600
	12/19/40	880	2.39	1.22	.097							1400	0	46.1	2215
	12/20/40	545	1.82	1.42	.056	5.16	2.99	2.17	23.3	10.3	7.5	1400	0	45.8	3300
	12/21/40	330	1.78	1.01	.060							1060	0	45.6	2325
	12/22/40	455	1.64	.79	.046							900	0	44.4	2400
	Total N_2		11.12									5% Amigen			
	Av. daily		2.56									1000 c.c.			
												I.V. daily			
2	12/23/40	755	2.75	1.98	.147	5.53	2.97	2.56	31.3	17.3	6.8	2200	6	44 7	3050
	12/24/40	1215	6.62	4.64	.279							1400	6	44.5	3600
	12/25/40	1195	7.52	4.97	.478							1200	6	45	2600
	12/26/40	880	8.43	6.72	.475	4.92	2.29	2.63	53	24	8.0	1200	6	43	2000
	12/27/40	820	7.43	6.54	.308							1200	6	42	3100
	Total N_2		32.75									Total N_2 30			
	Av. daily		6.55									Av. daily 6.0			
3	12/28/40	1010	5 13	4.38	.252	5.38	3.14	2.24	73	54	9.3				
	12/29/40	1030	5.77	4 69	.224							1400	0	41.2	5000
	12/30/40	1125	4.39	2.80	.127							1200	0	42.2	2200
	12/31/40	1320	4.09	2.69	.093	5.45	2.72	2 93	56	33	8.7	1300	0	43.0	3950
	Total N_2		19.38									1335	0	43.3	3500
	Av. daily		4.84												

TABLE IV. NITROGEN BALANCE STUDY ATTENDING THE INTRAVENOUS ADMINISTRATION OF PARENAMINE

J. B., U. H. No. 703888, appendicitis

		URINE				BLOOD									
PERIOD	DATE	VOL. (C.C.)	TOTAL N_2 (GM.)	UREA N_2 (GM.)	AMINO ACID N_2 (GM.)	TOTAL PROTEIN (GM. %)	ALBUMIN (GM. %)	GLOBULIN (GM. %)	UREA N_2 (MG. %)	N.P.N. (MG. %)	AMINO ACID (MG. %)	CAL. INTAKE	N_2 INTAKE (GM.)	WEIGHT (KG.)	FLUID INTAKE (C.C.)
1	3/18/41	3785	4.16	3.94	.246							1460	0	60.8	4650
	3/19/41	3030	3.18	.939	.276	7.13	3.97	3.16	4.7	21.6	5.7	1448	0	60.1	4400
	3/20/41	3430	3.18	.892	.261							1436	0	60.0	3650
	Total N_2		10.52									Parenamine I.V. daily			
	Av. daily		3.51												
2	3/21/41	3915	5.44	3.33	.458	6.85	4.04	2.81	5.0	24.3	7.7	1840	6.15	59.8	5600
	3/22/41	3055	6.32	3.48	.379							1578	6.15	60.4	5100
	3/23/41	3845	7.92	4.69	.400							1600	6.15	61.0	5400
	3/24/41	3715	9.99	6.59	.473	6.25	3.72	2.53	9.3	30	7.8	1700	6.15	60.5	5300
	3/25/41	3885	9.29	4.34	.415							1800	6.15	60.3	5100
	Total N_2		38.96								Total N_2		30.75		
	Av. daily		7.79								Av. daily		6.15		
3	3/26/41	3355	7.72	3.93	.309	5.84	2.41	3.43	13.5	30	6.0	1426	0	60.6	3950
	3/27/41	3425	4.72	2.81	.315							1446	0	59.3	4350
	3/28/41	2685	4.00	2.90	.234	6.01	3.80	2.21	12.0	29.0	6.25	1460	0	58.8	3450
	3/29/41	955	3.05	2.09	.115								0	57.3	2200
	3/30/41	1695	3.85	2.31	.188								0	57.8	2475
	Total N_2		23.34												
	Av. daily		4.67												

4. This patient, J. B. (U. H. No. 703888), a 68-year-old man, developed a small bowel obstruction subsequent to peritonitis from a ruptured appendix. This necessitated a decompressive enterostomy. The obstruction would recur when the enterostomy tube was clamped, or when oral feedings were allowed. For this reason, a period of parenteral feedings was elected. During the illness, the patient had lost twenty-eight pounds amounting to 18 per cent of his normal body weight. In this study 6.15 Gm. of nitrogen daily, in the casein digest

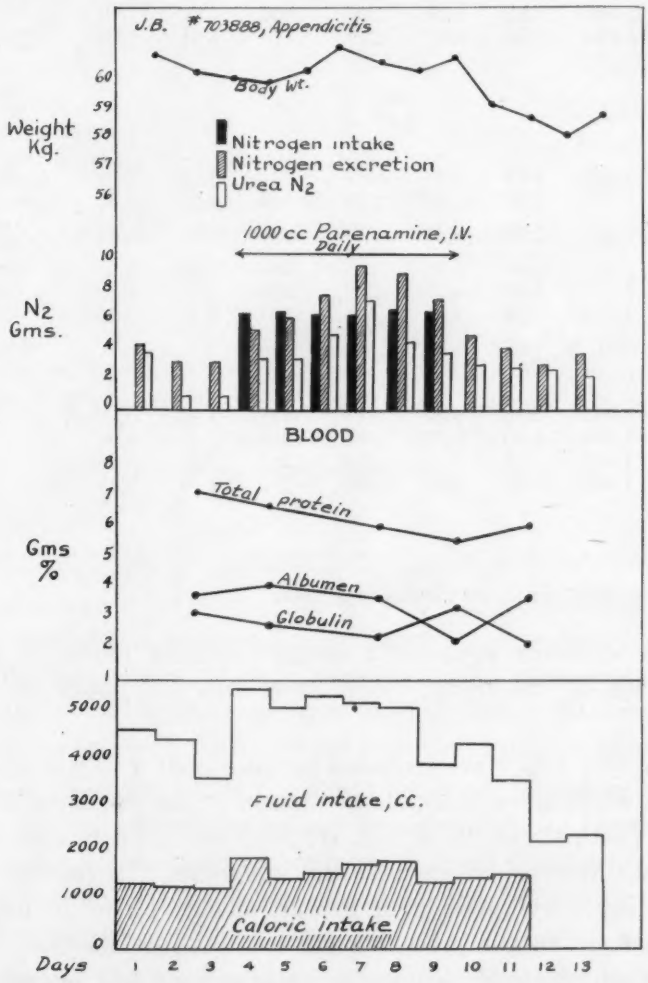

Fig. 4.—Nitrogen balance study attending intravenous administration of parenamine.

parenamine, given intravenously during Period 2, failed to produce positive nitrogen balance. It was noted (Tables III and IV) that the major portion of increased urinary nitrogen during the injection period was not amino acid nitrogen, although a slight increase of urine amino acid nitrogen did occur. This was more noticeable in Table III. The blood amino acid levels remained within normal limits throughout both studies. These determinations were done, however, from eight to twelve hours after injection of the casein digest and do not reflect the amino acid level during administration of the material. In

TABLE V. NITROGEN BALANCE STUDIES ATTENDING W. J., U. H. No. 773121, aged

PERIOD	DATE (1947)	URINE VOL. (C.C.)	SP. GR.	TOTAL N_2 (GM.)	UREA N_2 (GM.)	AMINO ACID N_2 (GM.)	AMMONIA N_2 (GM.)	CREATININE (GM.)	INTAKE SUGAR (GM.)	VENOUS PR. CM. H_2O	NITROGEN INTAKE (GM.)	I.V. WHOLE BLOOD C.C.	GM. N_2	AGE (DAYS)	CAL. INTAKE	FLUID INTAKE (C.C.)
1	1/14	2180	1.005	11.70	7.02	.227	.366	1.09	2.79	8	0				2000	4600
	1/15	5295	1.001	7.25	6.00	.290	.344	1.27	7.70		0				2000	5800
	1/16	4425	1.003	7.66	6.62	.244	.176	1.64	3.63		0				1840	5000
2	1/17	5130	1.002	8.98	6.83	.447	.246	1.39	5.08			490	13.2	2	1850	4500
	1/18	3420	1.003	5.13	4.04	.220	.054	1.27	12.65			425	10.1	2	1600	4600
	1/19}*											490	12.15	3	1840	4800
	1/20}	9940	1.003	12.98	9.43	.710	.458	3.08	16.47			490	10.78	3	1850	4800
	1/21	6150	1.001	6.33	5.78	.185	.369	1.38	2.02	5½		425	10.62	3	1600	4900
	1/22	5230	1.007	5.60	4.18	.262	.424	1.41	6.22			380	7.18	3	1440	3900
	1/23	4900	1.003	5.29	4.00	.131	.261	1.21	4.10			425	8.50	3	1800	4600
			Total N_2	44.31							Total N_2	72.53				
			Av. daily	6.33							Av. daily	10.36				
3	1/24	2900	1.002	5.22	4.85	.218	.211	1.45	5.70	7	0				1720	4300
	1/25	3540	1.005	5.80	4.77	.071	.265	1.27	4.07		0				1680	4250
	1/26	4500	1.003	4.73	3.16	.113	.405	1.44	3.06		0				1680	4900
	1/27	4280	1.003	4.84	4.07	.598	.212	1.07	2.19	6.0	0				1600	4500

*Urine specimens over two days collected together.

Table III some azotemia apparently resulted during Period 2 which abated at the completion of the study. This effect was not noted in other studies with amigen.

In Table V and Fig. 5 are recorded the results of a nitrogen balance study on a patient in whom the sole source of protein intake consisted of whole blood transfusions. This patient, W. J. (U. H. No. 773121), a 65-year-old man, was admitted to the University Hospital with a diagnosis of carcinoma of the stomach. He had lost thirty pounds in weight, amounting to 20 per cent of his normal body weight, in the preceding six months. At the completion of this study, and without further preparation, the patient was operated upon (see Case 7, Chart 7), at which time a segment of lower ileum about 30 inches in length was resected because of obstructing metastatic carcinoma in that area.

During Period 1 the patient received no protein intake, the caloric intake being maintained by intravenous glucose solution. In Period 2 the patient received daily, in addition to the intravenous glucose, one bottle of whole blood preserved with citric acid dextrose mixture. All the blood given was three days old or less. Its total nitrogen content as determined on each specimen by macro Kjeldahl analysis is listed as the nitrogen intake. As noted during Period 2, this was associated with no increase in urinary nitrogen excretion.

THE INTRAVENOUS ADMINISTRATION OF WHOLE BLOOD
65 years, carcinoma of stomach

BLOOD												STOOL		
WEIGHT (KG.)	HB. (GM. %)	HEMATOCRIT	R.B.C.	TOTAL PROT. (GM. %)	ALBUMIN (GM. %)	GLOBULIN (GM. %)	UREA N_2 (MG. %)	PLASMA CL. (MG. %)	URIC ACID (MG. %)	PLASMA VOL. (L.)	BLOOD VOL. (L.)	RETICULOCYTES (%)	N_2 (GM.)	UROBILINOGEN (MG.)
55.9	13.3	42.5	4.07									0.7		
56.4														
55.6														
													Av. daily 0.5	31
55.0	12.8	41	4.2	6.50	4.12	2.36	16.8	590	2.5					
55.0														
55.4														
55.3	13.7	44	4.5	7.2	5.10	2.00	12.8	581	2.7	2.85	5.09			
56.2														
56.4														
55												1.0		
													Av. daily 0.11	7.1
54.5	16.8	53.5	5.8	7.6	4.70	1.57	12.0	510	2.6	2.86	6.15			
55.8														
55.0														
54.6	16.3	54.0	5.8	7.2	4.24	2.10	11.6	617	2.8	2.50	5.42			
													Av. daily 0.19	49.0

The slightly downward trend of urinary nitrogen excretion started on the first day of Period 1 is continued throughout the experiment until the end of Period 3. By the criteria of total nitrogen intake plotted against output, the patient was in marked positive nitrogen balance during the six-day period when whole blood transfusions constituted the sole source of protein intake.

No clinical ill effects due to the mild plethora produced by transfusion were noted either subjectively by the patient or objectively by physical examination. The venous pressure remained within normal limits throughout the experiment. Subjectively the patient felt stronger and his mental outlook was much more cheerful following the blood transfusions.

Unfortunately the specimens for blood volume determination on Jan. 17, 1947, were lost, and blood volume changes are known for only the last four days of Period 2. However, the changes here were quite definite. The blood volume increased entirely by virtue of increased red cell mass, with the plasma volume remaining constant and then falling somewhat after the transfusions were stopped. Also in Period 3 there was a fall in total circulating hemoglobin, although the hemoglobin and hematocrit levels remained fairly constant. From these data it appears that most of the injected plasma proteins contained in the whole blood soon leave the circulation, whereas all of the hemoglobin or red blood cells injected can be accounted for by an increase in the blood volume

and, more particularly, its red blood cell component. Studies of the urobilinogen content of the stool, in an effort to demonstrate increased red blood cell destruction, were inconclusive. Although a definite increase was shown in Period 3, the total amounts are so small as to cast doubt as to their validity. Because the oral intake was restricted to only clear liquids, the amount of stool passed was quite meager. This may have been a factor in the results obtained.

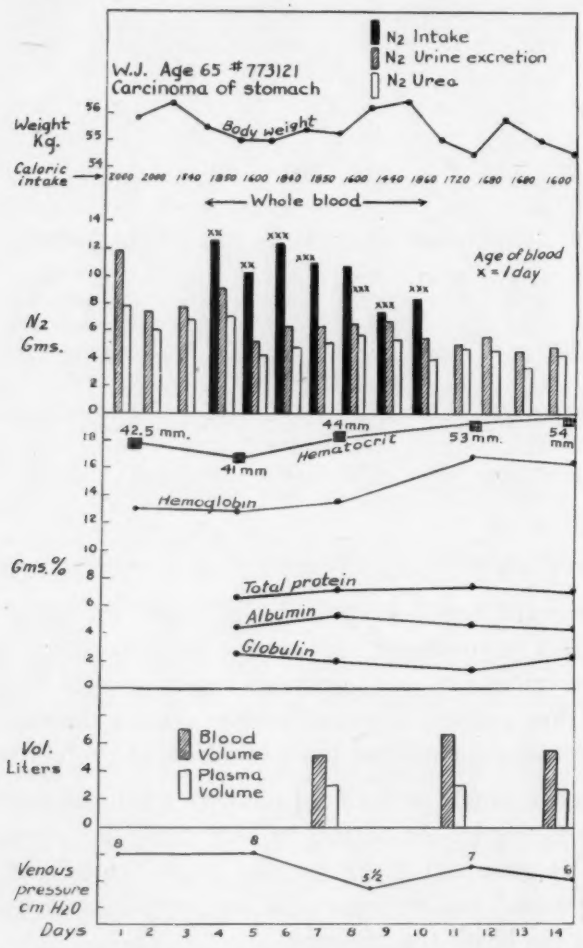

Fig. 5.—Nitrogen balance study attending the intravenous administration of whole blood.

Since it has been shown by Flink and Skubi,[68] Ross and Chapin,[174] and others[14] that there is an increased destruction of stored citrated blood following its transfusion, as compared to fresh blood, a study as tabulated in Table VI and Fig. 6 was carried out. This patient, J. T. (U. H. No. 775120), a 66-year-old man, was admitted to the University Hospital with a diagnosis of carcinoma of the esophageal gastric junction. He had lost forty-five pounds, amounting to 30 per cent of his normal body weight, and was unable to maintain his nutrition by oral means. At the completion of this study the patient was operated upon (Case 9, Chart 9).

Results quite similar to those in W. J., Table V, Fig. 5, were obtained. Whereas in W. J., blood three days old or less was used for transfusion, in J. T., all transfused blood was seven days old or more. During Period 2 no augmentation of urinary nitrogen excretion over Period 1, when only glucose was given, was noted. Also in the succeeding days, Period 3, there was no increased urinary nitrogen excretion over the preliminary basal period. On the contrary, the nitrogen conservation in Period 3 is considerably more efficient than

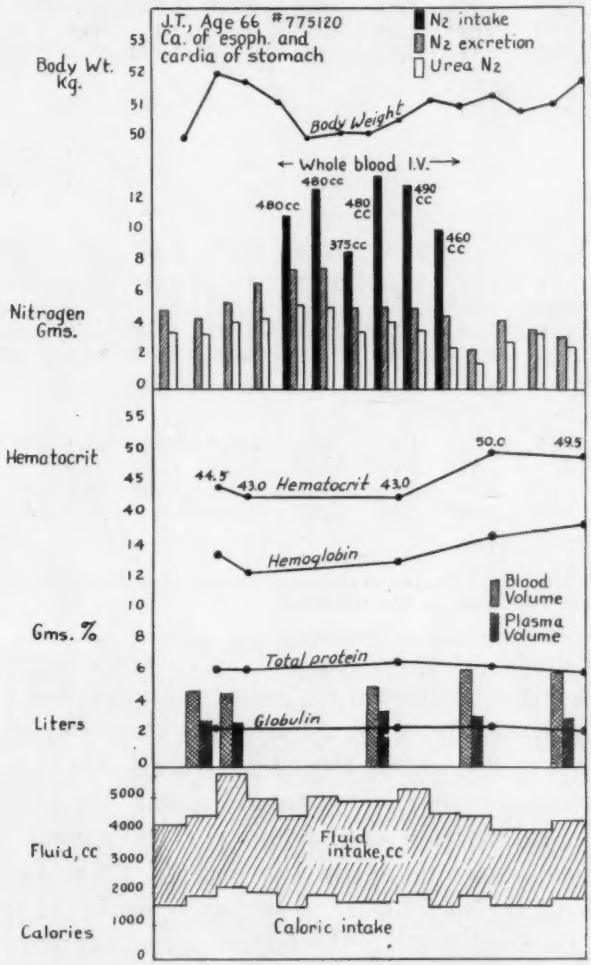

Fig. 6.—Nitrogen balance study attending the intravenous administration of whole blood.

during Period 1, as noted by respective figures of 14.53 as the total nitrogen excretion in the four days of Period 3 as against 22.15 for the four days of Period 1. Again during Period 2, if one considers only total nitrogen intake, marked positive nitrogen balance resulted.

The effect of the transfusions was quite closely mirrored by changes in the patient's blood. Ninety per cent of the transfused red blood cells can be accounted for by the increased blood volume and total red cell mass. Plasma volume changes were less marked, with about 50 per cent of the total plasma

TABLE VI. NITROGEN BALANCE STUDY ATTENDING
J. T., U. H. No. 775120, aged 66 years,

		URINE								INTAKE				
											I.V. WHOLE BLOOD			
PERIOD	DATE (1947)	VOL. (C.C.)	SP. GR.	TOTAL N_2 (GM.)	UREA N_2 (GM.)	AMINO ACID N_2 (GM.)	AMMONIA N_2 (GM.)	CREATININE (GM.)	SUGAR (GM.)	NITROGEN INTAKE (GM.)	C.C.	GM. N_2	AGE (DAYS)	CAL. INTAKE	FLUID INTAKE (C.C.)
1	1/29	1950	1.002	5.29	3.83	0.247	0.380	0.917	1.13	0				1680	4200
	1/30	4300	1.005	4.47	3.71	0.245	0.593	0.774	36.1	0				1820	4550
	1/31	3140	1.006	5.53	4.29	0.298	0.226	1.162	30.8	0				2280	5700
	2/1	3500	1.007	6.86	4.61	0.409	0.466	1.400	24	0				2000	5000
		Total N_2		22.15											
		Av. daily		5.54											
	2/2	6680	1.007	15.49	10.79	1.358	1.358	2.406	71	480		11.28	8	1632	4480
	2/3									480		12.62	9	1850	5080
2	2/4	2300	1.010	5.15	3.87	0.287	0.127	0.759	23.8	375		8.81	8	1700	5000
	2/5	3000	1.010	5.22	4.39	0.120	0.261	0.990	37.5	480		13.68	7	1700	5000
	2/6	3650	1.008	5.00	3.82	0.438	0.467	1.200	50.9	490		13.08	7	1900	5400
	2/7	3100	1.002	4.71	2.63	0.583	0.930	0.992	14.6	460		10.02	7	1600	4600
		Total N_2		35.57						69.49					
		Av. daily		5.93						11.58					
3	2/8	2960	1.006	2.55	1.83	0.207	0.530	0.829	26.1	0				1800	4500
	2/9	3400	1.003	4.21	3.06	0.340	0.340	1.258	12.8	0				1600	4000
	2/10	3800	1.005	3.99	3.83	0.342	0.247	1.102	30.4	0				1600	4000
	2/11	2250	1.012	3.78	2.78	0.203	0.339			0				1760	4400
		Total N_2		14.53						0					
		Av. daily		3.63						0					

*Urine collected over two days as one specimen.

protein contained in the donor blood or their equivalent having left the circulation. Again the stool urobilinogen studies were inconclusive probably for the same reasons as in the study of W. J., although there was an increase noted in Periods 2 and 3 over the control, Period 1. During this fourteen-day period, while nutrition was maintained by parenteral means, the patient's weight remained constant. Subjectively and objectively the patient felt better and stronger than he had before the study was started. From data on Mrs. C. N. (Case 6, Chart 6, U. H. No. 775502), a similar retention of transfused hemoglobin occurred. On Feb. 5, 1947, the following findings were noted. Hemoglobin was 5.6 Gm. per cent, hematocrit was 23.5, plasma volume was 2.18 L., and blood volume 2.84 L. The total circulating hemoglobin (5.6 by 2.84 by 10) was 159 Gm. In the next five days, she received 4,500 c.c. of whole blood by transfusion. On Feb. 10, 1947, the patient's hemoglobin was 16.5 Gm. per cent, hematocrit was 58.5, the plasma volume was unchanged at 2.18 L. The total blood volume was 5.29 L. The total circulating hemoglobin (16.5 by 5.29 by 10) was 872 Gm. Assuming the donor blood to contain 15 Gm. of hemoglobin per 100 c.c., 675 Gm. of hemoglobin were administered. Allowing for errors in technique this constitutes complete retention of transfused red blood cells in the circulation.

THE INTRAVENOUS ADMINISTRATION OF WHOLE BLOOD
carcinoma of esophagus and cardia of stomach

	BLOOD												STOOL	
WEIGHT (KG.)	HB. (GM. %)	HEMATOCRIT	R.B.C.	TOTAL PROT. (GM. %)	ALBUMIN (GM. %)	GLOBULIN (GM. %)	UREA N_2 (MG. %)	PLASMA CL. (MG. %)	URIC ACID (MG. %)	PLASMA VOL. (L.)	BLOOD VOL. (L.)	RETICULOCYTES (%)	N (GM.)	UROBILOGEN (MG.)
50												1.4		
52	13.7	44.5	4.72	6.2	3.74	2.50	10.0	564	2.5	2.77	4.99			
51.8	12.6	43.0	4.56	6.2						2.49	4.37			
51.2												1.1		
													0.893	21.6
													0.223	5.4
50.0														
50.2														
50.2														
50.6	13.15	43.0	4.5	6.6	3.52	2.54	14.1	598	2.5	3.14	5.50			
51.2														
51.0												0.6		
													3.82	106.8
													.64	17.8
51.4	14.7	50	5.32	6.4	3.28	2.70	9.0	600	3.0	3.11	6.22			
50.9														
51.0														
50.8	15.5	49.5	5.26	6.0	3.4	2.36	11.4	550	3.0	3.14	6.21			
													1.05	84.4
													.26	21.1

Table VII and Fig. 7 show the results of a nitrogen balance study attending the intravenous administration of whole blood and amigen separately. The patient, T. A. (U. H. No. 773207), was a 53-year-old woman admitted to the University Hospital with a carcinoma at the outlet of the stomach producing complete obstruction. The patient had been unable to take and retain any food by mouth. She had lost thirty-five pounds in weight, amounting to 25 per cent loss of her normal body weight. The study was terminated on the third postoperative day after a gastric resection when it became possible for the patient to take food by mouth again (see Case 4, Chart 4).

During Period 1, while the patient was receiving no protein, the urinary nitrogen excretion averaged 4.8 Gm. per day. When the patient received 500 c.c. of whole blood daily, in addition to 3,000 c.c. of 10 per cent glucose intravenously, the urinary nitrogen excretion remained close to the basal level. In Period 3 when the patient received 24 Gm. of nitrogen daily as 4,000 c.c. of 5 per cent amigen in 5 per cent glucose solution, a marked rise of urinary nitrogen excretion resulted. However, there still occurred a fairly strong positive nitrogen balance with the amigen, an average daily urinary nitrogen excretion of 18.98 Gm. against an average daily nitrogen intake of 24 Gm. associated with the administration of intravenous amigen. In Period 3, there

was a weight gain of three kilograms. This is not a true weight gain, but a retention of water by the body. Such an effect has been noted in other instances when large amounts of amigen have been given intravenously. It does not appear to be due to sodium chloride effect alone for the sodium chloride content of amigen as given by the manufacturer is 3 per cent of the dried powder. For 200 Gm. of amigen, the amount given in this experiment, this would make a sodium chloride intake of 6 Gm. per day, an amount hardly enough to produce edema in a patient with apparently normal renal function.

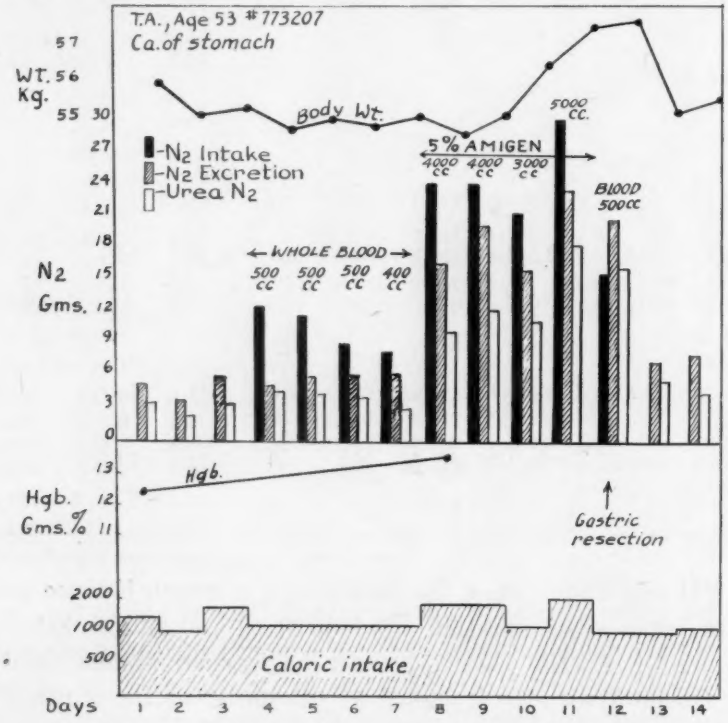

Fig. 7.—Nitrogen balance study attending the intravenous administration of whole blood and amigen.

Tables VIII and IX, Figs. 8 and 9, show the results of two similar studies. E. E. (U. H. No. 764398) was a 59-year-old white man who in the preceding eight months had noticed marked asthenia, loss of appetite, and a weight loss of one hundred pounds, amounting to thirty-five per cent of his normal body weight. On admission to the hospital, x-ray examination revealed a large carcinoma of the stomach producing a high-grade obstruction at the gastric outlet. C. A. (U. H. No. 768842) was a 64-year-old white man with a carcinoma involving the upper third of the esophagus. The patient had been unable to take any food other than small amounts of clear liquids by mouth for the preceding two weeks. Symptoms in all were of about six months' duration. During this time, the patient had lost fifty pounds, amounting to 30 per cent of his usual body weight. After a preliminary period of zero nitrogen intake, 3,000 c.c. of 5 per cent amigen in 5 per cent glucose solution containing 18 Gm.

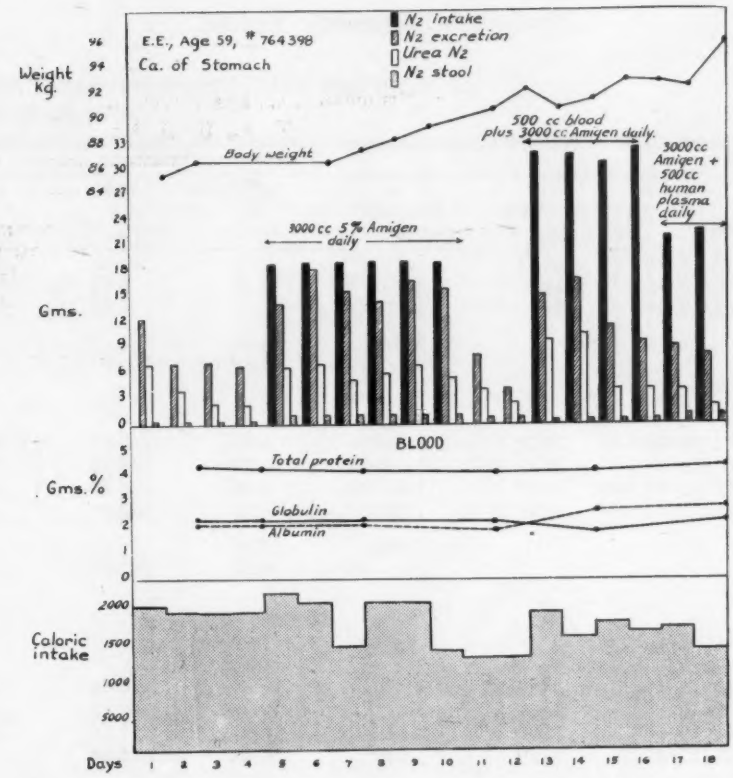

Fig. 8.—Nitrogen balance study attending the intravenous use of amigen, human plasma, and whole blood.

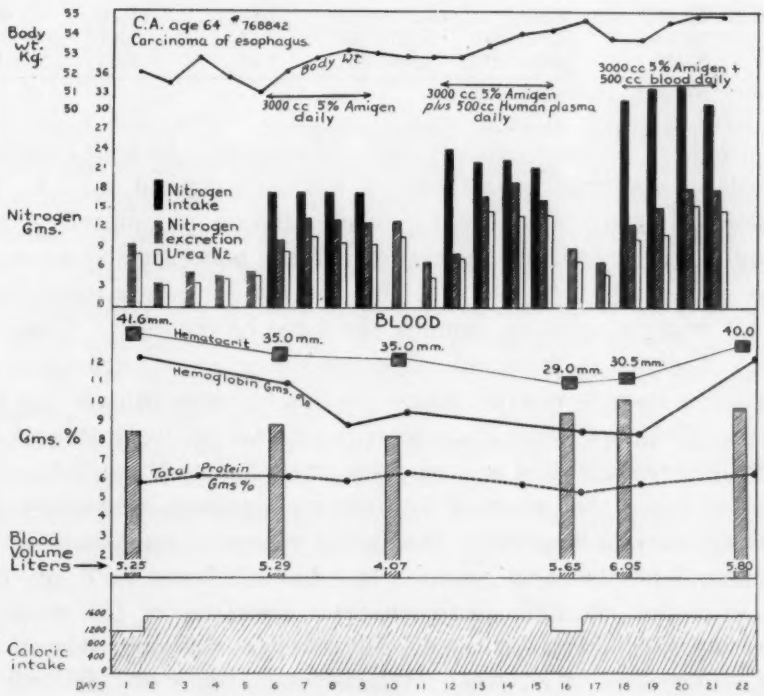

Fig. 9.—Nitrogen balance study attending the intravenous administration of amigen, human plasma, and whole blood.

TABLE VII. NITROGEN BALANCE STUDY ATTENDING THE T. A., U. H. No. 773207, aged

				OUTPUT			
PERIOD	DATE	VOLUME (C.C.)	SPECIFIC GRAVITY	TOTAL N_2 (GM.)	UREA N_2 (GM.)	AMINO ACID (GM.)	CREATININE (GM.)
1	12/ 7/46	1490	1.012	5.16	3.39	0.450	1.340
	12/ 8/46	1620	1.005	3.67	2.61	0.98	0.810
	12/ 9/46	4690	1.011	5.47	3.75	1.20	1.870
			Total	14.30			
			Av. daily	4.86			
	12/10/46	3170	1.012	4.82	3.85	0.190	1.080
2	12/11/46	2550	1.005	5.92	4.19	0.630	0.765
	12/12/46	2690	1.005	5.98	3.79	1.23	0.646
	12/13/46	2890	1.006	5.95	2.97	1.67	0.434
			Total	22.67			
			Av. daily	5.53			
3	12/14/46	2430	1.012	16.67	10.64	3.600	1.940
	12/15/46	2300	1.017	19.96	12.18	2.980	1.47
	12/16/46	2230	1.012	15.97	11.09	2.39	1.27
	12/17/46	3160	1.012	23.31	18.07	2.27	1.07
			Total	75.91			
			Av. daily	18.98			
4	12/18/46*	3115	1.021	20.87	15.78	3.19	1.31
	12/19/46	2140	1.008	7.48	5.47	0.77	0.984
	12/20/46	1540	1.006	7.99	4.54	1.35	1.108

*Day of operation, gastric resection.

of nitrogen were given intravenously daily (Period 2). In both studies positive nitrogen balance was obtained, although it was more marked in C. A., Table IX. As happens uniformly when giving casein digests parenterally, there is a pyramiding of urinary nitrogen excretion. When using smaller amounts of the digest (see Tables II, III, and IV), this increased nitrogen excretion was so marked that positive nitrogen balance could not be obtained. However, when the amount of digest is increased, although the urinary nitrogen excretion is also increased, a stage is reached where positive nitrogen balance can uniformly be obtained. This had been achieved without fail in five instances where 18 Gm. of nitrogen contained in amigen were given daily. From Tables VIII and IX, it can be noted that most of the increased urinary nitrogen excretion is not in the amino acid fraction. This latter fraction increases only when excessively large amounts of amigen are given too rapidly as in T. A., Table VII, when up to 3 Gm. of amino acid nitrogen appeared in the urine. In the days following the administration of amigen, the urinary nitrogen excretion promptly returned to its original level, although for a day following the injection of amigen there may be some increased urinary nitrogen loss. When amigen is administered in conjunction with human plasma (Period 5, Table

INTRAVENOUS ADMINISTRATION OF WHOLE BLOOD AND AMIGEN
53 years, carcinoma of stomach

INTAKE						BLOOD	
AMMONIA N_2 (GM.)	SUGAR (GM.)	NITROGEN INTAKE (GM.)	CALORIC INTAKE	FLUID INTAKE	WEIGHT (KG.)	H.B. (GM.)	TOTAL PROTEIN (GM.)
1.082	28.2	0	1400	4000	56	12.5	6.3
0.972	19.2	0	1000	3200	55.2		
1.08	49.1	0	1760	4450	55.4		
		I.V. WHOLE BLOOD					
		GM. N_2 | VOL. (C.C.)					
0.713	29.4	12.305 500	1200	4100	54.8		
0.650	12.0	11.685 500	1200	4350	55.0		
0.37	19.0	9.820 500	1200	3800	54.9		
0.208	35.1	7.320 400	1200	3975	55.2		
	Total	41.30					
	Av. daily	10.280					
		I.V. AMIGEN					
		GM. N_2					
1.510	11.79	24.0	1750	5000	54.6	13.6	7.5
1.85	11.85	24.0	1750	4500	55.2		
1.85	10.8	18.0	1200	3700	56.6		
1.52	12.9	30.0	2000	5400	57.6		
	Total	96.0					
	Av. daily	24.0					
		I.V. BLOOD					
1.91	67.9	15.05	1000	3400	57.8		
1.37	26.5	0	1000	3400	55.2		
0.88	2.14	0	1100	3700	55.6		

VIII; Period 4, Table IX), a more marked positive nitrogen balance results. The urinary nitrogen excretion while getting amigen plus plasma was slightly higher in Table IX and slightly lower in Table VIII than when getting amigen alone. However, the results obtained in Period 5, Table VIII, may not reflect a true state of affairs, for during this period the urinary volume decreased markedly, the patient gained three kilograms and developed mild edema. Following this period the patient's condition became precarious and the study had to be discontinued. Nitrogen retention is even more marked when amigen plus whole blood is given (Table VIII, Period 4; Table IX, Period 6). Here again the urinary nitrogen loss remains about at the same level as with amigen alone, whereas the nitrogen intake is markedly increased. In Period 6, Table IX, only about 66 per cent of the injected hemoglobin from the 2,000 c.c. of blood given can be accounted for by an increase of hemoglobin level and blood volume. The cause of the anemia which developed during the study (Table IX) is not definite. It may only partially be explained on the basis of blood loss due to repeated blood specimens taken for analysis which amounted to 450 c.c. removed by Aug. 15, 1946. There were no other known sources of blood loss and examination of the stools showed no marked loss by that avenue.

TABLE VIII. NITROGEN BALANCE STUDY ATTENDING THE INTRAVENOUS ADMIN

E. E., U. H. No. 764398, aged 59 yea

		URINE							
PERIOD	DATE	VOLUME (C.C.)	SPECIFIC GRAVITY	TOTAL N_2 (GM.)	UREA N_2 (GM.)	AMINO ACID N_2 (GM.)	CREATININE (GM.)	AMMONIA N_2 (GM.)	SUGAR (GM.)
1	4/12/46	1680	1.022	12.56	6.8	0.47	1.02	0.59	7.3
	4/13/46	1640	1.010	7.3	3.9	0.1	0.71	0.35	1.8
	4/14/46	2140	1.012	7.5	2.5	0.0	0.77	0.47	7.9
	4/15/46	2280	1.005	6.7	2.2	0.103	0.63	0.51	2.0
			Total	34.06					Tota
			Av. daily	8.51					Av.
2	4/16/46	2470	1.010	14.3	6.6	0.395	0.84	0.34	5.1
	4/17/46	1880	1.017	18.1	7.3	0.27	0.85	0.40	4.2
	4/18/46	1550	1.013	15.43	5.6	0.18	0.81	0.36	4.2
	4/19/46	1880	1.018	14.86	6.0	0.29	0.77	0.40	5.7
	4/20/46	1990	1.020	17.9	7.1	0.26	0.79	1.25	0.5
	4/21/46	1430	1.020	16.12	5.7	0.20	0.72	0.97	0.3
			Total	96.71					Tot
			Av. daily	16.12					Av.
3	4/22/46	1350	1.020	8.6	4.5	0.2	0.614	0.58	1.7
	4/23/46	1015	1.012	4.37	2.5	0.1	0.426	0.35	1.1
									Tot
									Av.
4	4/24/46	2470	1.017	15.29	10.1	0.4	0.79	0.42	4.6
	4/25/46	2100	1.017	17.1	7.9	0.34	0.79	0.44	4.3
	4/26/46	1550	1.018	11.4	4.4	0.22	0.54	0.40	3.2
	4/27/46	1010	1.018	9.8	3.94	0.12	0.65	0.16	2.5
			Total	53.59					Tot
			Av. daily	13.39					Av.
5	4/28/46	840	1.015	9.22	3.2	0.13	0.42	0.126	2.5
	4/29/46	485	1.027	5.83	1.89	0.08	0.421	0.136	1.8
			Total	15.05					To
			Av. daily	7.52					Av

PRESENTATION OF CLINICAL CASES: CLINICAL RESULT OF THE PREPARATION BY PARENTERAL MEANS OF POOR-RISK PATIENTS FOR SURGERY

The following case histories are presented as representative of patients requiring preoperative preparation by parenteral feedings, either as the sole source of protein and caloric intake, or as a supplement to an inadequate oral intake. A record of the pulse and blood pressure during operation, and of the postoperative clinical course, is shown with each case history.

Case 1.—A. S., (U. H. No. 688258), a 65-year-old man, was admitted to the University of Minnesota Hospitals on Aug. 26, 1946, with a four-month history of having experienced a thirty pound weight loss amounting to 20 per cent loss of his normal body weight, anorexia, and a feeling of gaseous distress in the epigastrium. The patient had been unable to eat solid foods for one month prior to admission to the hospital. General physical examination revealed a pale appearing white man in no acute distress. Temperature

ADMINISTRATION OF AMIGEN, HUMAN PLASMA, AND WHOLE BLOOD

59 years, carcinoma of stomach

STOOL						BLOOD				
SUGAR (GM.)	TOTAL N_2 (GM.)	CALORIC INTAKE	N_2 INTAKE (GM.)	FLUID INTAKE (C.C.)	WEIGHT (KG.)	TOTAL PROTEIN (GM. %)	ALB. (GM. %)	GLOB. (GM. %)	UREA N_2 (MG. %)	URIC ACID (MG. %)
7.3		2002	0	3100	85.9					
1.8		1930	0	3500	86.8	4.38	2.15	2.23	12.8	4.5
7.9		1930	0	3400						
2.0		1930	0	3450		4.31	2.10	2.20	11.0	3.24
Total	1.78									
Av. daily	.44									
			I.V. 3000 C.C. 5% AMIGEN							
5.1		2367	18	4250						
4.2		2080	18	4000	86.8					
4.2		1460	18	3600	87.7	4.28	2.04	2.24	14	3.35
5.7		2080	18	4000	88.6					
0.5		2080	18	4000	89.5					
0.3		1488	18	4000						
Total	6.04	Total N_2	108.0							
Av. daily	1.01	Av. daily	18.0							
1.7		1296	0	2400	90.9	4.16	1.93	2.23	12.5	4.3
1.12		1296	0	2600	92.3					
Total	6.12		3000 5% AMIGEN I.V.	500 C.C. BLOOD I.V.						
Av. daily	.81									
4.62		1842	18	14.15	4000	91.1	4.22	1.95	2.27	11.0	3.5
4.3		1696	18	14.0	4000	91.6				
3.2		1746	18	13.3	3700	93 0				
2.5		1650	18	14.8	4200	93 0				
Total	2.44	Total N_2	128.25							
Av. daily	0.61	Av. daily	32.06							
			(PLASMA I.V.)							
2.5		1677	18	4.63	4600	92.7				
1.82		1425	18	4.81	4250	96.1	4.43	2.62	1.81	19
Total	2.08	Total N_2	45.44							
Av. daily	1.04	Av. daily	22.72							

was 98.6°F., pulse was 76 and blood pressure was 110/70 mm. Hg. There was a suggestive mass in the epigastrium, but no other abnormalities were noted on physical examination. Gastrointestinal x-ray studies revealed a large polypoid carcinoma of the stomach with considerable retention of barium after four hours. Hemoglobin on admission was 12.5 Gm. per cent, white blood count was 7,500 with a normal differential. Blood urea nitrogen was 15 mg. per cent, blood chlorides were 568, and total plasma proteins were 5.1 Gm. per cent. Urinalysis was negative.

The patient was prepared almost entirely by parenteral means. Whatever was taken by mouth was lost by gastric aspirations and vomitus. He received 3000 c.c. daily of 5 per cent amigen in 5 per cent glucose solution intravenously plus therapeutic doses of vitamin B, C, and K, for seven days. In addition, during this time, the patient received 500 c.c. of whole blood and 500 c.c. of human plasma.

On Sept. 3, 1946, the patient was operated upon. Exploration of the peritoneal cavity revealed a large carcinoma of the stomach with infiltration into the lesser omentum and involvement of lymph nodes along both curvatures. A gastric resection was performed removing about 80 per cent of the stomach and all palpable involved nodes. The operation

TABLE IX. NITROGEN BALANCE STUDY ATTENDING THE INTRAVENOUS
C. A., U. H. No. 768842, aged

		URINE								STOOL		
PERIOD	DATE (1946)	VOL. (C.C.)	SP. GR.	TOTAL N_2 (GM.)	UREA N_2 (GM.)	AMINO ACID N_2 (GM.)	CREATININE (GM.)	AMMONIA N_2 (GM.)	SUGAR (GM.)	TOTAL N_2 (GM.)		BLOOD DRAWN (C.C.)
1	7/31	2450	1.015	9.70	7.60	0.290	1.52	1.47	26.46			66
	8/1	1570	1.022	4.53	4.08	0.100	0.59	0.99	58.09			
	8/2	2930	1.013	5.89	4.10	0.162	0.64	1.55	23.19			20
	8/3	3840	1.013	5.52	4.56	0.261	1.34	1.70	82.17			
	8/4	1990	1.012	5.71	4.99	0.237	0.99	1.18	33.43			
		Total		31.35						Total	0.86	
		Av. daily		6.27						Av. daily	.17	
2	8/5	2450	1.010	10.05	7.35	0.382	0.71	1.41	2.11			86
	8/6	2400	1.006	13.93	11.10	0.266	1.01	1.23	1.73			
	8/7	2740	1.004	13.48	10.96	0.482	0.47	1.58	2.11			
	8/8	2860	1.007	13.38	10.81	0.295	0.83	1.15	3.09			20
		Total		50.84						Lost		
		Av. daily		12.71								
3	8/9	3450	1.005	13.58	11.30	0.173	0.90	2.00	4.35			86
	8/10	3350	1.005	7.14	4.76	0.184	0.97	1.27	1.71	0		
4	8/11	2940	1.004	8.38	6.40	0.188	0.91	1.54	1.85			66
	8/12	3470	1.005	17.14	14.99	0.413	1.01	1.70	2.78			
	8/13	3750	1.007	18.30	14.63	0.375	0.98	1.32	3.08			20
	8/14	2830	1.008	15.34	13.24	0.396	0.934	0.85	2.92			
		Total		59.16						Total	0.70	
		Av. daily		14.79						Av. daily	0.17	
5	8/15	2000	1.004	8.28	7.20	0.238	0.88	1.08	1.36			86
	8/16	3460	1.007	6.32	5.19	0.132	0.83	1.59	4.67			
		Total		14.60						Total	0.62	
		Av. daily		7.30						Av. daily	0.31	
6	8/17	2350	1.009	12.48	10.22	0.778	1.10	1.25	3.36			91
	8/18	3650	1.006	15.11	11.03	0.689	0.95	1.99	1.61			5
	8/19	3370	1.008	18.54	16.18	0.815	1.08	1.35	5.19			5
	8/20	3180	1.007	18.19	14.91	0.804	1.05	1.81	2.16			5
		Total		64.32						0		
		Av. daily		16.08								
	8/21											

lasted five and one-half hours, during which time the patient received 1000 c.c. of whole blood and 1000 c.c. of 5 per cent glucose solution. The patient's postoperative course was uneventful. His highest temperature was 101.6°F. by rectum on the first postoperative day. He was allowed out of bed on the first day after operation and left the hospital on the sixth postoperative day.

Case 2.—E. P. (U. H. No. 772109), a 49-year-old white woman, was admitted to the University of Minnesota Hospitals on November 5, 1946, and discharged Nov. 20, 1946. She gave a history that dated back one year when the onset of vomiting was first noted. At the start, this occurred chiefly at night, but as time went on it occurred after every meal. Along with the vomiting and a progressive weight loss, which amounted in all to about forty-five pounds or 30 per cent loss of her normal body weight, the patient noted epigastric distress and weakness.

ADMINISTRATION OF AMIGEN, HUMAN PLASMA, AND WHOLE BLOOD
64 years, carcinoma of esophagus

INTAKE					BLOOD								
NITROGEN INTAKE (GM.)	CAL. INTAKE (GM.)	FLUID INTAKE	WEIGHT (KG.)	HB. (GM. %)	HEMATOCRIT	TOTAL PROT. (GM. %)	ALBUMIN (GM. %)	GLOBULIN (GM. %)	UREA PLASMA N_2 (MG. %)	CL. (MG. %)	URIC ACID (MG. %)	VOL. (L.)
0	1200	3000	52.2	12.20	41.6	6.00	3.47	2.03	10.3	495	1.90	5.25
0	1600	4000	51.8									
0	1600	4000	53.0			6.25	3.55	1.97	12.8	570	2.28	
0	1600	4000	52.0									
0	1600	4000	51.2									
3000 c.c. 5% AMIGEN I.V.												
18	1600	4000	52.4	11.00	35.0	6.25	3.55	2.28	13.7	521	2.50	5.29
18	1600	4000	53.0									
18	1600	4000	53.4	9.00		6.00	3.67	2.14	15.0	602	2.90	
18	1600	4000	53.2									
Total 72.0												
Av. daily 18.0												
0	1600	4000	53.0	9.65	35.0	6.40	3.43	2.10	13.7	566	2.45	
3000 5% I.V. AMIGEN	500 c.c. I.V. HUMAN PLASMA											
18	6.15	1600	4500	53.0								
18	4.45	1600	4500	53.6								
18	4.60	1600	4500	54.2		5.90	2.93	2.08	13.7	586	2.00	
18	4.15	1600	4500	54.4								
Total 91.35												
Av. daily 22.84												
0	1200	3000	55.0	8.40	29.0	5.40	3.11	1.73	17.0	520	1.95	5.65
0	1600	4000	54.0									
3000 5% I.V. AMIGEN	500 c.c. I.V. BLOOD											
18	14.95	1600	4500	54.0	8.65	30.5	5.90	3.21	2.28	15.0	2.50	6.05
18	16.05	1600	4500	54.8								
18	16.75	1600	4500	55.2								
18	14.05	1600	4500	55.2								
Total 133.8												
Av. daily 33.45												
					12.05	40.0	6.20	3.55	2.00	24.0	2.21	5.80

General physical examination revealed a cooperative white woman showing evidence of recent weight loss. Blood pressure was 130/80 mm. Hg., pulse was 80, and temperature was 98.6° F. In the midepigastrium, a hard nontender mass about 7 cm. in diameter was noted. The remainder of the physical examination was essentially negative. Gastrointestinal x-ray examination revealed a large annular mass in the distal half of the stomach, past which barium flowed with only slight difficulty. Admission laboratory study revealed a negative urinalysis; hemoglobin was 10.4 Gm. per cent; white blood count was 7,350 with a normal differential. Blood urea nitrogen was 8 mg. per cent, blood chlorides were 658 mg. per cent, and total plasma proteins were 5.8 Gm. per cent. Preoperative preparation extended over a nine-day period during which time the patient received intravenously 3000 c.c. of 5 per cent amigen in 5 per cent glucose solution plus therapeutic doses of vitamins B, C, and K, added to the fluids daily. In addition, during this time, the patient received three transfusions of whole blood, a total of 1,500 c.c. Oral intake consisted of University Hospital

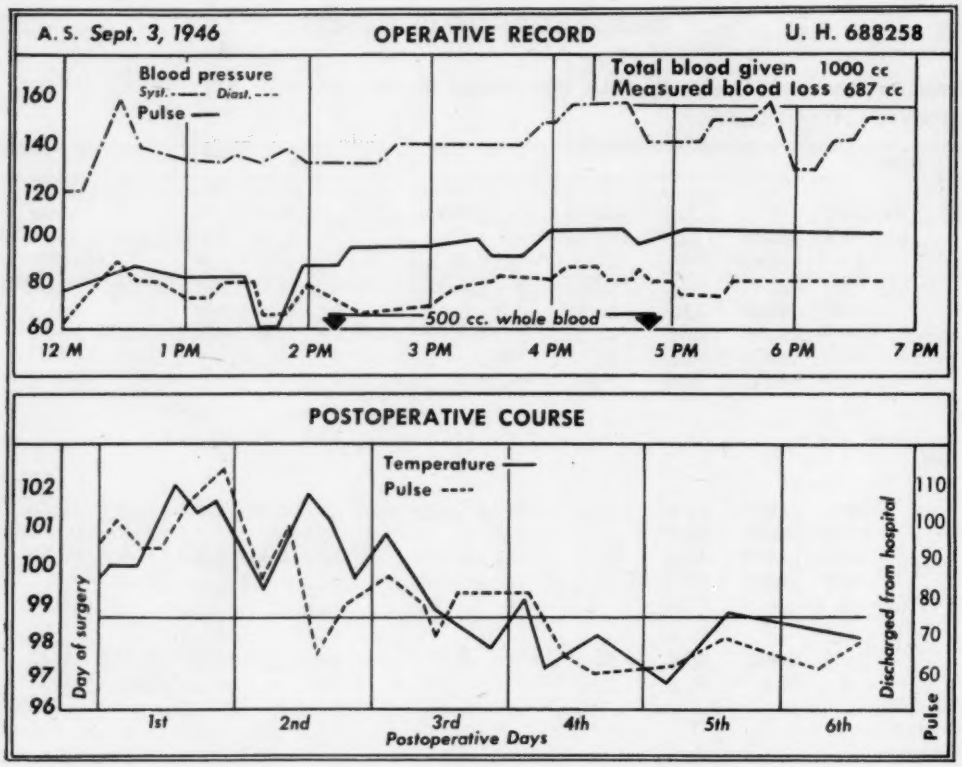

Chart 1.

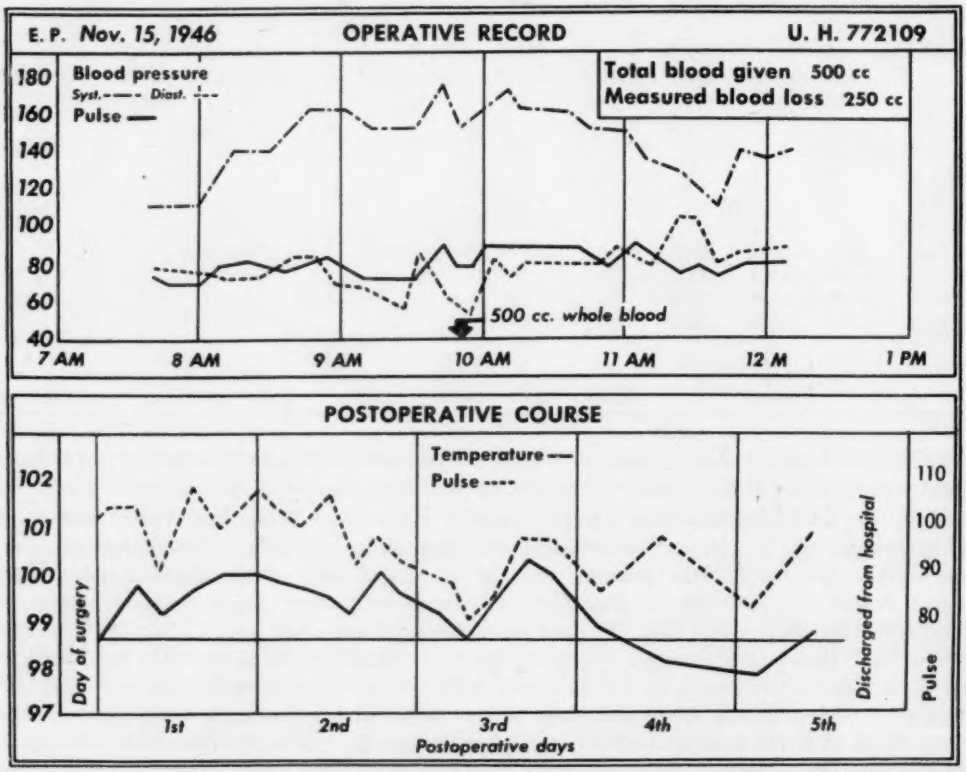

Chart 2.

Diet 2[204] in amounts from 500 to 1,500 c.c. daily, plus about 500 c.c. of water and fruit juice. However, at least one-half of the daily oral intake was lost by vomiting or gastric aspirations and at times almost the entire oral intake was lost. During this period the patient's weight increased from 51 kilograms on November 6, to 54.6 kilograms on November 14, the day before surgery.

Nov. 15, 1946, the patient was operated upon. A large carcinoma involving the lower half of the stomach was found. A gastric resection removing 75 per cent of the stomach was carried out. In addition, since the gall bladder contained numerous stones, it was removed, and an appendectomy was also performed. The operation lasted four hours during which time the patient received 500 c.c. of whole blood. The measured blood loss was 250 c.c.

The postoperative course was smooth and uncomplicated. The patient was allowed out of bed on the first postoperative day and left the hospital on the fifth postoperative day.

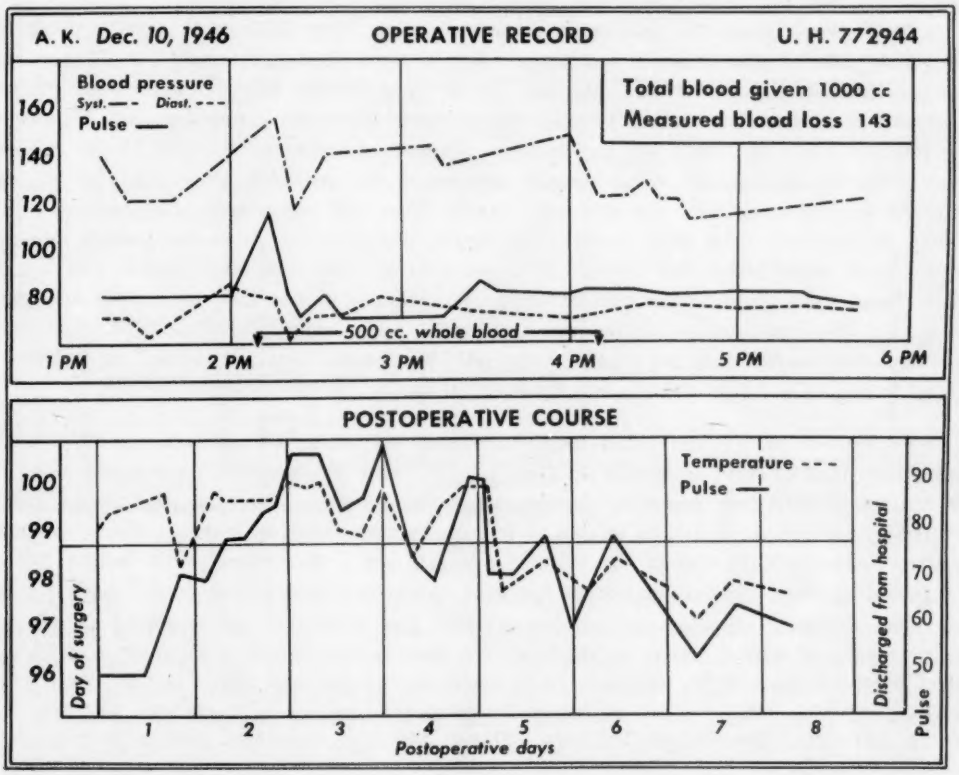

Chart 3.

Case 3.—A. K. (U. H. No. 772944), a 60-year-old woman was admitted to the University of Minnesota Hospitals on Nov. 30, 1946. The illness at time of admission dated back about seven months when the patient first became aware of vague epigastric pains and distress and of a sense of early satiety after eating. These symptoms became progressively more marked, to be followed by progressive weight loss, amounting to a total loss of fifty pounds during the illness or about 30 per cent of her normal weight, and increasingly frequent spells of vomiting. There had been no melena or hematemesis. For the month preceding admission to the hospital the patient had noted a mass in the epigastrium, which was especially prominent after eating.

General physical examination revealed a fairly comfortable, stoical, white woman. Although there was evidence of weight loss as noted by loose flabby skin, the patient did not appear markedly emaciated. Blood pressure was 130/74 mm. Hg., pulse was 72, and tempera-

ture 98.6° F. The only finding of note on physical examination was a large, firm, nontender mass in the left upper quadrant, about 8 by 16 cm. in diameter. Gastrointestinal x-ray studies on three occasions revealed an extremely dilated stomach with many retained food particles and an area of complete obstruction at the pylorus. On three examinations it was impossible to get sufficient barium past the obstructing lesion, so that a diagnosis other than high-grade obstruction could be made. Laboratory studies revealed a negative urinalysis, hemoglobin was 10.3 Gm. per cent, white blood count was 4,300 with a normal differential. Blood urea nitrogen was 17 mg. per cent and the total plasma proteins were 4.9 Gm. per cent. For nine days the patient received 3000 c.c. of 5 per cent amigen in 5 per cent glucose solution, plus therapeutic doses of vitamins B, C, and K, daily. In addition, during the nine-day preoperative preparation period, the patient received 1,500 c.c. of whole blood. The patient took about 1,000 c.c. of University Hospital Diet 2 daily by mouth, but over one-half of this was vomited or removed by aspirations.

On Dec. 10, 1946, the patient was operated upon. An obstructing carcinoma of the prepyloric area of the stomach was found with a huge dilated stomach. A 75 per cent gastric resection was performed. Because of the huge dilated stomach filled with particulate matter, it became necessary to open the stomach during the operation and suction off the retained material. This was not entirely successful because of the size of the retained food particles, and finally using a gall bladder scoop, scoopful after scoopful of this material was removed from the stomach. Aside from this irregularity, the operation proceeded uneventfully. In all it lasted four hours, during which time the patient received 1000 c.c. of whole blood and 500 c.c. of 5 per cent glucose solution. Another 500 c.c. of whole blood were given to the patient after she returned to the floor to sustain her blood pressure. The postoperative course was uneventful and uncomplicated. The highest postoperative temperature was 100.2° F. by rectum. The patient was allowed out of bed on the second postoperative day, and she left the hospital on the eighth postoperative day.

Case 4.—T. A. (U. H. No. 773208), a 53-year-old white woman, was admitted to the University of Minnesota Hospitals on Dec. 4, 1946, with a history of nausea and vomiting of one-month duration, becoming progressively more severe. For the two weeks before admission, the patient had been unable to retain anything taken by mouth. There had been a fifteen pound weight loss in the preceding month and a thirty-five pound weight loss in the preceding three months, amounting to about 25 per cent loss of her normal body weight.

On admission, physical examination revealed the patient to be somewhat dehydrated with evidence of marked recent weight loss. Her temperature was 98.8°F., pulse was 85, and blood pressure was 126/88 mm. Hg. Admission hemoglobin was 12.5 Gm. per cent, white blood count was 6,000 with a normal differential distribution. Blood urea nitrogen was 19 mg. per cent. Blood chlorides were 566 mg. per cent and total plasma proteins were 6.3 Gm. per cent.

The patient was unable to retain anything taken by mouth except small sips of water. Gastrointestinal x-ray study revealed a dilated stomach with complete obstruction in the pyloric area and the duodenum could not be visualized. The patient was placed on a nitrogen balance study (see Table VII, Fig. 7) prepared by intravenous amigen and whole blood and was operated upon Dec. 18, 1946. Exploration of the abdomen revealed an extensive carcinoma of the antrum of the stomach extending beyond the serosa. There were extensive metastases to the liver which I estimated to replace about 50 per cent of the liver tissue. In addition, there were numerous grossly involved lymph nodes extending along the greater and lesser curvatures of the stomach. However, because of the complete obstruction of the stomach, palliative gastric resection was decided upon. A 75 per cent gastric resection was carried out. The operation lasted 4.5 hours during which time 500 c.c. of whole blood and 1000 c.c. of 5 per cent glucose solution in distilled water were given. The postoperative course was routine and uneventful. The patient was allowed out of bed on the day after surgery, and each day thereafter for increasingly longer periods. The

indwelling nasoduodenal tube which had been placed into the afferent loop of the gastrojejunal anastomosis at the time of surgery was removed on the third postoperative day and the patient left the hospital on the fifth postoperative day.

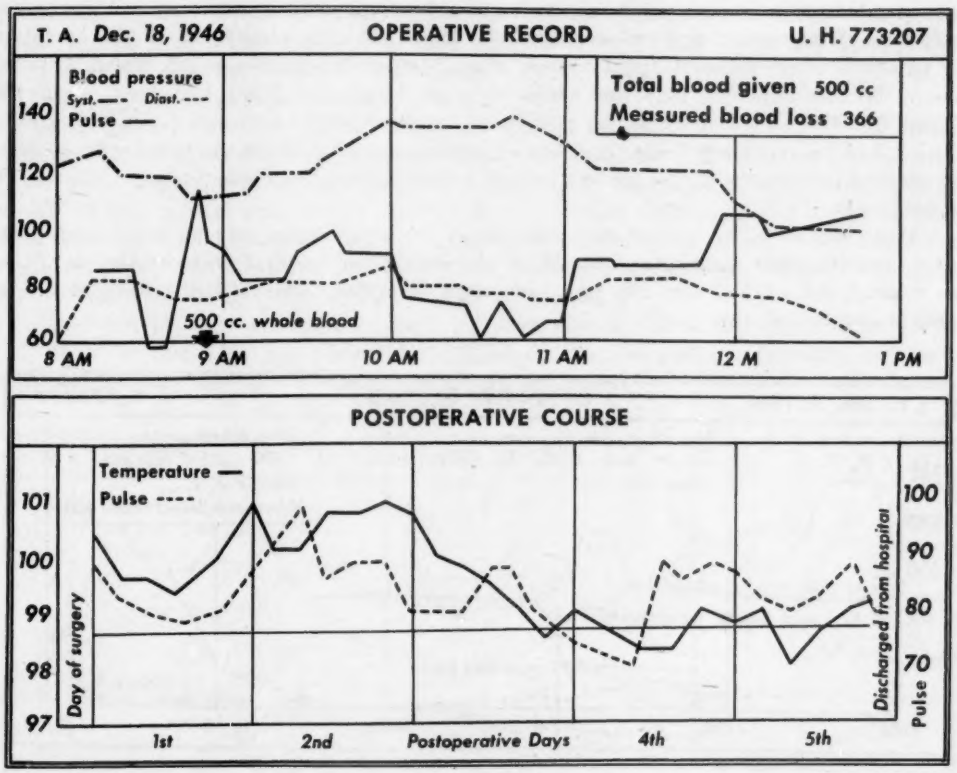

Chart 4.

Case 5.—E. B. (U. H. No. 773802), a 89-year-old white woman, was admitted to the University of Minnesota Hospitals on Jan. 7, 1947, with a history of increasing weakness, a fifty pound weight loss amounting to 33 per cent loss of her usual body weight, and constipation becoming increasingly more severe during the preceding six months. For the past six weeks, the patient had been unable to retain any solid food taken orally. A diagnosis of pernicious-like anemia had been made by one physician. Liver and iron therapy had been instituted, but in spite of this her course had been progressively downhill.

General physical examination on admission revealed an emaciated, moderately dehydrated, white woman. Blood pressure was 120/80 mm. Hg. pulse was 100, temperature was 98.6° F. There was a large, nodular mass in the right upper quadrant of the abdomen apparently separate from the liver. Barium enema x-ray study revealed a constricting carcinoma of the hepatic flexure of the colon associated with the palpable mass described. Gastrointestinal study revealed a normal stomach with some distortion of the duodenum believed to be due to extrinsic pressure. Laboratory studies revealed a negative urinalysis. Hemoglobin level was 10.6 Gm. per cent; white blood count was 17,000 with 70 per cent polymorphonuclear cells, 25 per cent lymphocytes, 2 per cent monocytes, and 3 per cent eosinophiles. Blood urea nitrogen was 24 mg. per cent; blood chlorides were 578 mg. per cent, and total plasma protein level was 5.4 Gm. per cent. After the diagnosis was established and a decision was made to operate upon the patient, an intensive course of parenteral preoperative preparation was started on Jan. 20, 1947. The patient was able to take from 500 to 800 c.c. of University Hospital Diet 2 orally daily, but vomited over one-half of the

amount taken each day, and at times she retained practically none of the oral intake. Tube feedings were attempted, but this was unsuccessful because of vomiting. The patient received 1500 c.c. of 5 per cent amigen in 5 per cent glucose solution intravenously daily and a total of 2000 c.c. of whole blood during this period. On Jan. 31, 1947, the patient was operated upon.* A right hemicolectomy and end-to-end ileotransverse colostomy was performed. The operative procedure lasted 3.5 hours. At the completion of the operation, the patient's blood pressure fell to shock levels, despite a transfusion of blood. At this time it became apparent that the needle through which the blood had been given had slipped from the vein and the major portion of the transfused blood and 5 per cent glucose solution had inadvertently been administered subcutaneously. When another bottle of blood was started intravenously, the patient rallied promptly and the blood pressure returned to normal levels.

Postoperatively the patient did very nicely. Convalescence was uncomplicated. The highest postoperative temperature was 101.6° F. rectally on the first postoperative day. She was allowed out of bed this day and each day thereafter. She left the hospital on the tenth postoperative day.

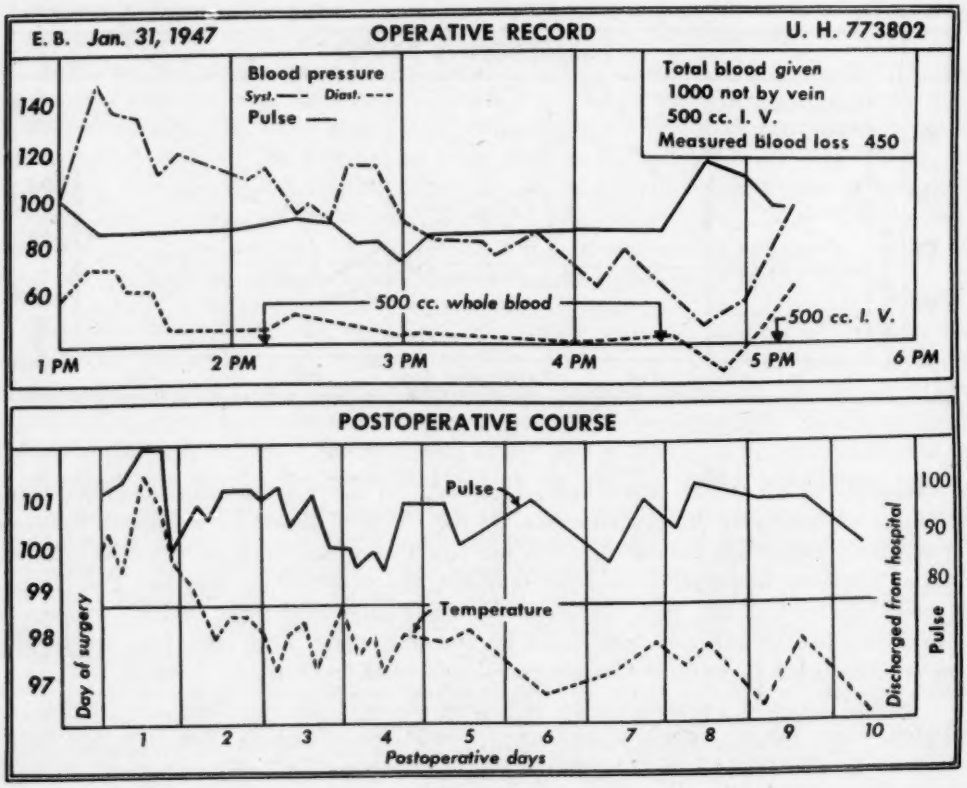

Chart 5.

Case 6.—W. J. (U. H. No. 773121) was a man admitted to the University of Minnesota Hospitals on Jan. 7, 1947, and discharged Feb. 4, 1947. He gave a history of vague epigastric pain and distress over the preceding six months associated with anorexia, weakness, and a weight loss of thirty pounds amounting to about 20 per cent of his usual body weight.

General physical examination revealed a comfortable somewhat emaciated white man. Blood pressure was 140/70 mm. Hg. pulse rate was 75 per minute, and temperature was 98.6° F. No abnormalities were noted on physical examination. Gastrointestinal x-ray study

*Operation was done by Dr. Fred Kolouch.

revealed an extensive carcinoma of the stomach. While in the hospital, the patient developed symptoms of small bowel obstruction, successfully treated by Miller-Abbott, small bowel, intubation suction. At the termination of this episode, the patient was placed on a nitrogen balance study (Table V, Fig. 5) during which time the patient's only source of protein intake consisted of whole blood transfusions. The remainder of the nutritional requirements were met by intravenous glucose and vitamins B, C, and K. The only thing allowed by mouth was sweetened strained fruit juice. At the completion of this study, Jan. 29, 1947, the patient was operated upon.

Exploration of the peritoneal cavity revealed an extensive carcinoma of the stomach involving the esophagus. There were numerous carcinomatous metastases in the mesentery of the small bowel where it joins the gut. In the lower ileum two of these metastases had become annular and obstructed the bowel. As a palliative measure, about thirty inches of lower ileum with the obstructing sites of tumor were resected, and an end-to-end anastomosis was performed. The operation lasted 2.5 hours, during which time the patient received 500 c.c. of whole blood slowly. The measured blood loss was 53 c.c.

The patient's postoperative course was uncomplicated. The highest temperature was 100° F. by rectum. He was allowed out of bed on the first postoperative day, and on the sixth postoperative day he was discharged from the hospital.

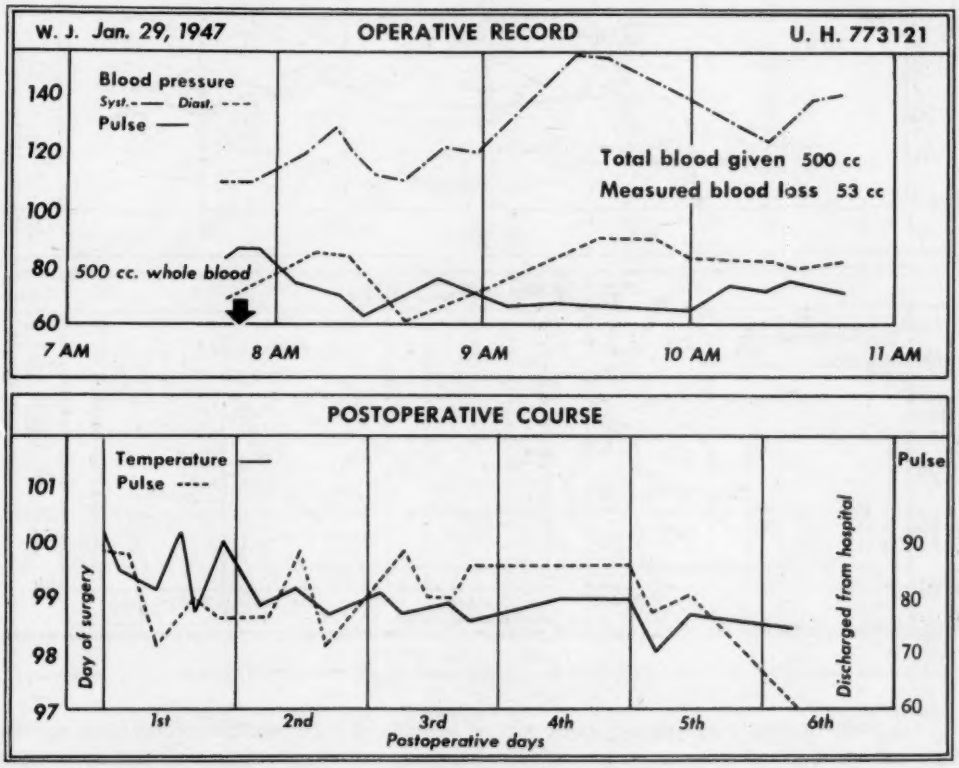

Chart 6.

Case 7.—C. N. (U. H. No. 775502), a 69-year-old woman, was admitted to the University of Minnesota Hospitals on Feb. 4, 1947. For the preceding year she had noticed a mass in the right upper quadrant of the abdomen, which had slowly progressed in size. In all, the patient had lost thirty pounds in weight, amounting to 30 per cent of her normal body weight.

General physical examination revealed an extremely emaciated, elderly, white woman. Blood pressure was 130/80 mm. Hg, pulse rate was 75, and temperature was 98.6° F. The

only positive finding aside from the emaciation was a mass in the right upper abdomen about 6 cm. in diameter and apparently fixed to the liver. Laboratory studies revealed a negative urinalysis. Hemoglobin level was 5.2 Gm. per cent, red blood cell count was 3,140,000, and white blood cell count was 10,200. The blood urea nitrogen was 10 mg. per cent, blood chlorides were 634 mg. per cent, and total plasma proteins were 6.7 Gm. per cent. Barium enema x-ray study revealed a carcinoma involving the hepatic flexure of the colon. The patient was prepared for surgery by massive blood transfusions, receiving from February 5 to February 10, a total of 4500 c.c. of whole blood. Prior to starting transfusions, blood study revealed a hemoglobin level of 5.6 Gm. per cent; hematocrit reading was 23.5, plasma volume was 2.18 L., and blood volume was 2.84 L. After receiving 4500 c.c. of whole blood, repeat blood studies revealed a hemoglobin level of 16.5 Gm. per cent, a hematocrit of 58.5, a plasma volume of 2.19 L., and a blood volume of 5.29 L. In addition to the whole blood transfusions, the patient took by mouth 1000 to 1500 c.c. of University Hospital diet.

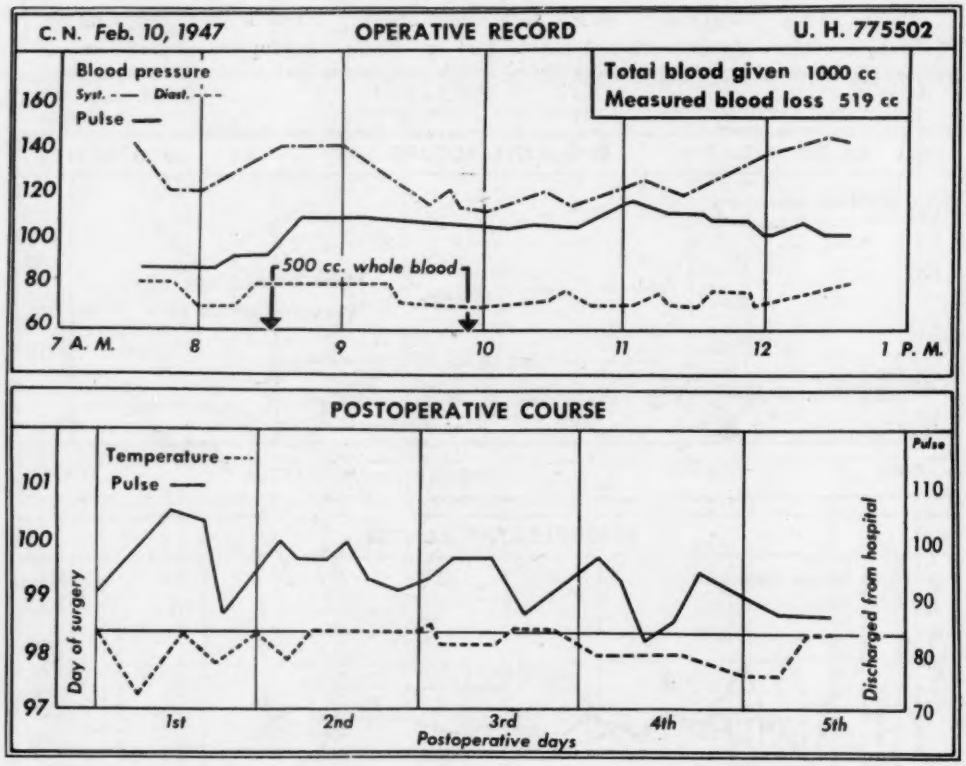

Chart 7.

On Feb. 10, 1947, the patient was operated upon.* A right hemicolectomy with excision of 20 cm. of terminal ileum and an end-to-end ileotransverse colostomy was performed. The operation lasted 4.5 hours, during which time the patient received 1000 c.c. of whole blood and 1000 c.c. of 5 per cent glucose in distilled water.

The patient's postoperative course was uneventful. The highest postoperative temperature was 98.6° F. the day after surgery, and she was discharged from the hospital on the fifth postoperative day.

Case 8.—B. T. (U. H. No. 775215), a 75-year-old white man, was admitted to the University of Minnesota Hospitals on Jan. 24, 1947. The patient apparently had been in

*Operation was done by Dr. Owen H. Wangensteen.

good health until two months prior to admission to the hospital at which time he had first noticed loss of appetite, progressively increasing weakness, and vague epigastric pain. During the period of his illness, the patient lost forty-five pounds amounting to 30 per cent of his normal body weight. General physical examination revealed a poorly nourished white man who appeared apathetic and listless, but who did not appear to be in any acute distress. Temperature was 100.4° F., pulse rate was 100, blood pressure was 110/60 mm. Hg. The remainder of the physical examination was essentially negative. Gastrointestinal x-ray studies revealed a carcinoma of the antrum of the stomach producing a fairly high-grade obstruction. Urinalysis on admission was negative, hemoglobin level was 10.9 Gm. per cent, and white blood count was 15,000. Blood urea nitrogen level was 18 mg. per cent, blood chlorides were 611 mg. per cent, total plasma proteins were 6.4 Gm. per cent. During the patient's stay on the medical service, the patient continued to have a tachycardia up to 120 per minute. Clinically the patient appeared to be a poor risk for surgery. However,

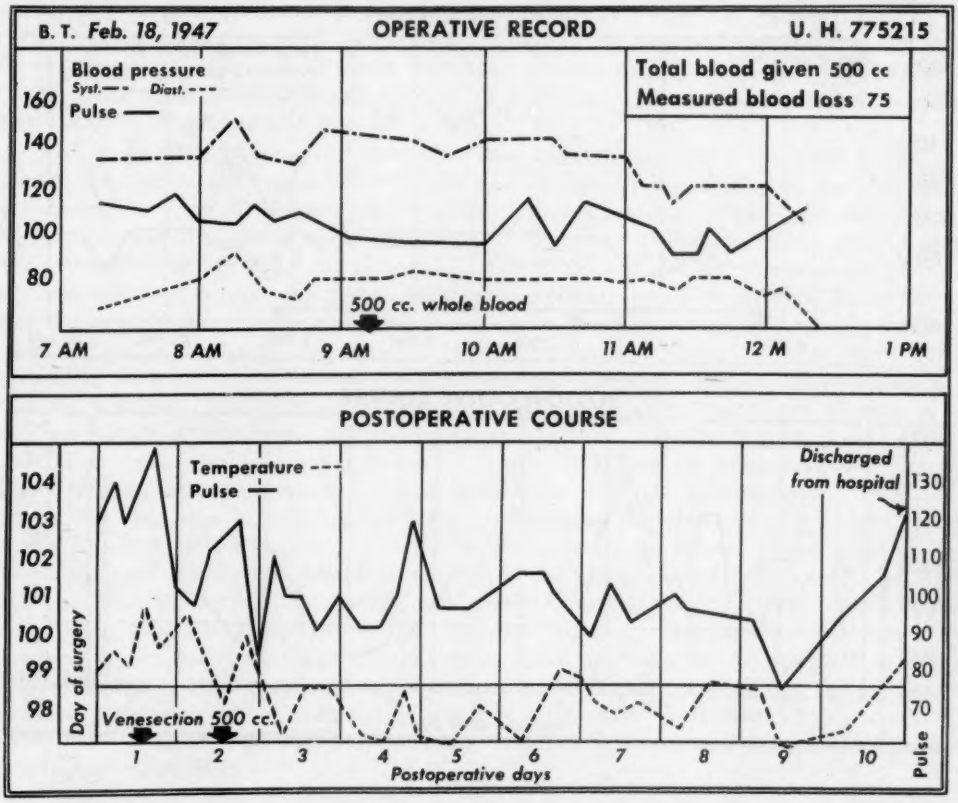

Chart 8.

because of the presence of malignant disease, surgical therapy was decided upon, and on February 6 an active period of preoperative preparation was begun. During the twelve-day period, from February 6 to 17, the patient received daily either 500 or 1000 c.c. of whole blood, a total of 6500 c.c. of whole blood being given during this period. The patient took 600 to 1000 c.c. of University Hospital Diet 2 orally, but most of it was lost by emesis or removed by gastric aspiration. During this period, the patient's weight increased from 52.2 to 57 kilograms; his hemoglobin increased to 18.8 Gm. per cent with a hematocrit of 64 on Feb. 17, 1947.

On Feb. 18, 1947, the patient was operated upon. A carcinoma of the distal one-half of the stomach was found, and a 75 per cent gastric resection was performed. The opera-

tion was uncomplicated. It lasted four hours and ten minutes, during which time the patient received 500 c.c. of whole blood. The measured blood loss was 73 c.c.

On the first postoperative day, the patient's general condition was complicated by a persistent tachycardia up to 130 and a moderate amount of dyspnea. Because of the markedly elevated hemoglobin and hematocrit, a venesection drawing off 500 c.c. of blood was performed on February 19. This produced very definite improvement in both respiration and pulse. Next day, since the hemoglobin level was still elevated at 17.9 with a hematocrit of 62.4, the venesection was repeated again removing 500 c.c. of blood. From this day onward the convalescence was uncomplicated except for a mild icterus which first appeared on February 24 and cleared in two days. This was not associated with any laboratory findings of liver damage. The patient was allowed out of bed on the second postoperative day, and left the hospital on the eleventh postoperative day.

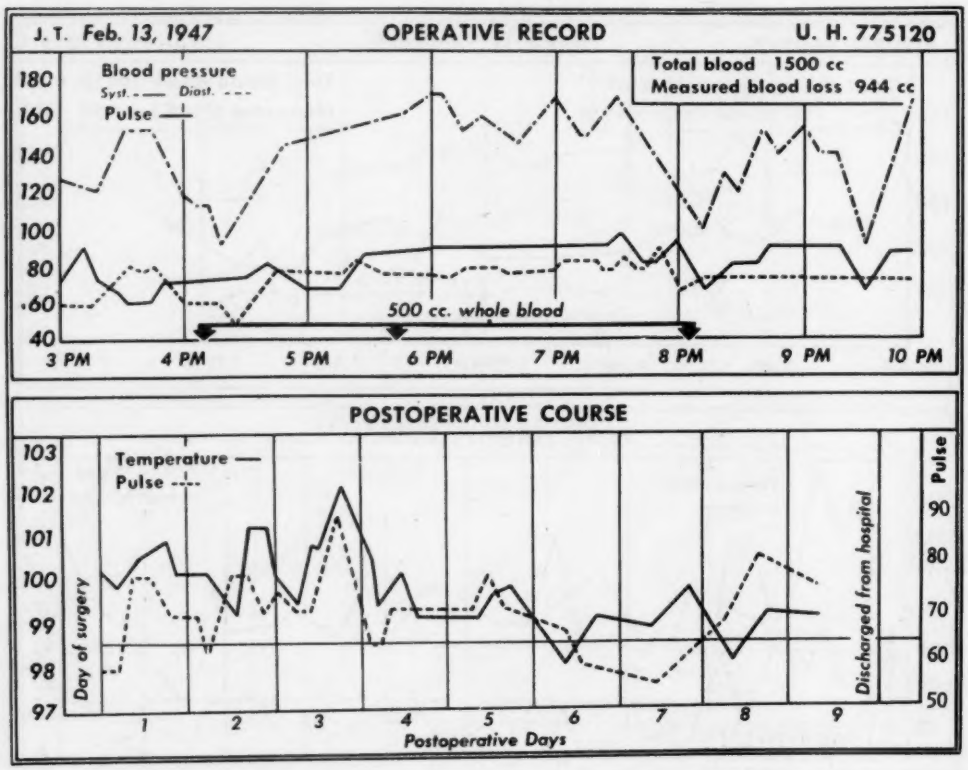

Chart 9.

Case 9.—J. T. (U. H. No. 775120), was a man who was admitted to the University of Minnesota Hospitals on Jan. 28, 1947. The illness at the time of admission had begun about six months previously with difficulty in swallowing solid foods as the first symptom. This became progressively more marked as time went on. More recently there was noted some difficulty in the swallowing of liquid foods also. In addition, the patient experienced vague, indefinite, epigastric pain becoming more severe during the illness. In all, there was noted a forty-five pound weight loss amounting to 30 per cent loss of his normal body weight.

Physical examination on admission revealed a somewhat emaciated, comfortable, and cooperative white man. Blood pressure was 140/70 mm. Hg, pulse rate was 70, temperature was 98.6° F. There were no gross abnormalities noted on examination. Gastrointestinal x-ray study revealed a definite constricting lesion of the lower esophagus associated with

a filling defect of the upper portion of the stomach. Although the lesion produced considerable obstruction to the lower esophagus, barium could be seen going past the site of narrowing.

The patient was started on a nitrogen balance study on Jan. 29, 1947 (see Chart 9, Fig. 6), receiving whole blood daily as the only source of nitrogenous intake. In addition, the patient received 3000 c.c. of 10 per cent glucose intravenously, also sweetened fruit juice by mouth ad libitum. At the completion of the study on Feb. 13, 1947, the patient was operated upon.

At operation exploration of the abdomen was carried out through a transverse upper abdominal incision, at which time the diagnosis of carcinoma of the upper stomach and esophagus was confirmed. The lesion appeared to be operable and no distant metastases were noted. The incision was then extended across the eighth costal cartilage and out into the seventh left intercostal space, entering the left pleural cavity. The left diaphragm was then incised from the area of the incision down to the esophageal hiatus. Resection of the upper one-half of the stomach and lower one-third of the esophagus was carried out. The residual stomach was then mobilized and anastomosed in the chest with the proximal esophagus. In all, the operation lasted six hours and forty minutes during which time the patient received 1500 c.c. of whole blood and 1500 c.c. of 5 per cent glucose solution in distilled water. The measured blood loss was 944 c.c.

All in all the patient withstood this long difficult operation very well. The postoperative course in the hospital was smooth and apparently uncomplicated, and the patient was discharged from the hospital on the ninth postoperative day. Four days later, however, the patient was readmitted to the hospital in an acutely dehydrated state and in shock. For the preceding two days the patient had been vomiting and had been unable to retain anything taken by mouth. He responded to prompt treatment of intravenous saline solution, glucose, and plasma. X-ray studies of the abdomen revealed several dilated loops of small intestine, and a tentative diagnosis of paralytic ileus was made. During the night of admission, however, the patient passed some bloody material by rectum; on rectal examination the next day, bloody material could be noted on the examining finger whereas it had not been noted on admission. On abdominal examination, moderate distention was observed and the abdomen was somewhat more rigid than it had been on admission. The drainage from the nasogastric tube which had been passed had a definite feculent odor. In addition, during this time, the patient developed signs of vascular insufficiency to the right leg and foot with a line of demarcation appearing in the mid-calf. A clinical diagnosis of probable mesenteric thrombosis was made, and in spite of the precarious state of the patient, operation was decided upon. Exploration was carried out on Feb. 26, 1946. At abdominal exploration, gangrene of the entire small intestine beginning four inches distal to the ligament of Treitz and extending to about four inches proximal to the ileocecal orifice was noted. Resection without spillage of the entire involved small intestine and end-to-end anastomosis of the residual eight inches of small intestine were performed. The patient withstood this operation but left the operating room in a precarious state and died about twenty-four hours later.

Post-mortem examination revealed the esophagogastric anastomosis to be perfectly intact and well healed. The heart was normal, but the aorta was involved by extensive atherosclerosis. In the thoracic and upper abdominal aorta there were two large thrombi about two inches in length. These were the probable source of emboli which migrated into the superior mesenteric artery and the right femoral artery.

This group of nine poor-risk patients, all of whom had lost from 20 to 33 per cent of their normal weight, were prepared for operation principally by parenteral feedings. All survived an operation of major magnitude with two postoperative complications occurring in the group.

One complication occurred in J. T. (Case 9), who developed a thrombosis on a markedly atherosclerotic aorta which may well have occurred independently

of the preoperative preparation or the operation. However, the possibility remains that the repeated blood transfusions may have augmented the known increased tendency of blood to clot postoperatively and so have produced this accident. The aortic thrombosis may have occurred early in the postoperative course with the mesenteric embolism occurring much later. Nevertheless, the patient did survive a long and difficult operation; the operative wound and anastomosis healed per primam, bearing testimony that at least functionally the protein metabolic processes were operating normally.

The other complication, that of B. T. (Case 8), was definitely related to overenthusiastic use of blood transfusions. When it was appreciated that incipient circulatory failure was resulting from the persistent plethora, and venesection was done, prompt improvement resulted. From this case, as well as C. N. (Case 6), and from balance studies V and VI, it should be appreciated that whole blood transfusions will produce increases in blood volume directly proportional to the amount of blood given, and that this increase is almost entirely in the cellular component of the blood. Almost all of the transfused red blood cells remain in the circulation at least for the first few days after transfusion. For this reason, in an instance where there are no avenues of blood loss, daily whole blood transfusions should not be kept up indefinitely. However, it should also be pointed out that patients seem to tolerate a mild plethora very well. It may even have a cushioning effect on withstanding the trauma of the operation.

DISCUSSION

From nitrogen balance studies attending the use of whole blood intravenously, as the sole source of protein intake, it was noted that uniformly no increase of urinary nitrogen excretion occurred over that noted during a preliminary basal period. In this respect whole blood behaves as does whole human plasma. In contradistinction to this response, the intravenous use of casein digests are uniformly attended with a marked pyramiding of urinary nitrogen excretion as noted in these studies and as reported by others.[12, 24, 61, 115, 129, 139, 194] From this difference in type of response, it would appear that there is a fundamental difference in the manner of utilization of these materials by the body. That this variation could be explained on the basis of time factor is entirely possible. The protein digests are apparently utilized and deaminized in a short period of time. Hence, the end results of their metabolism appear directly as an increase in urinary nitrogen excretion. On the other hand, plasma protein does not appear to be catabolized directly. It apparently leaves the circulation and becomes a part of the general body protein stores to be available on call as needed by the over-all protein economy of the body. The fact that its use is not attended by an increased urinary nitrogen excretion is further evidence that it is not broken up into its constituent amino acids as has been similarly postulated by Whipple and his coworkers.[99, 103, 128] From the work of Schoenheimer and associates[182] it appears that the half life of plasma protein is about two weeks. It may take that long for the normal course of protein metabolism to bring about the catabolism of

the injected plasma protein. Elman and Davey[62] reported a delayed urinary nitrogen excretion after giving plasma intravenously to dogs, while at the time of plasma infusion no augmentation of urinary nitrogen was evident and marked positive nitrogen balance was present. However, it is also true that as the protein stores of the body are depleted, extreme conservation of available bodily nitrogen material occurs, whereas when the protein stores of the body are in a more normal state this conservation is not as marked.[23, 97, 155] In the studies herein reported, although the follow-up time was not long, no evidence of delayed nitrogen excretion after plasma infusions was noted. Certainly it would appear that plasma protein given intravenously soon leaves the circulation and becomes part of the general body protein pool and as such is utilized and slowly replaced in the continuing metabolism of the body.

With the use of whole blood for nutritional purposes, additional factors are at play. From the evidence presented, it appears that the red blood cells injected remain in the circulation and as such they probably do not directly partake of the general body protein economy. That there are no reservoirs outside of the circulation where red blood cells can be sequestered has been shown by the work of Ross and Chapin[173] and Hahn and associates[83] using red blood cells tagged with radioactive iron.

However, the red blood cells in themselves may constitute a pool of protein which on their inevitable disintegration becomes available for the body needs. With an increase of red blood cell mass, more cells will eventually disintegrate and more protein for general bodily use will be liberated. Eventually all of the injected red blood cells must disintegrate and their contained protein becomes liberated for general body needs. This is a continuing process. When the total circulating red cell mass is raised, more cells are available which have reached the end of their life span and are disintegrated. That no increased urinary nitrogen excretion is evident when the red cell mass is increased must indicate that the proteins so liberated are reutilized by the body. By supplying preformed red blood cells to the body, the protein which, as shown by Robscheit-Robbins and her co-workers,[167, 169] would by first priority have been used for building new hemoglobin is thereby spared and is available for other body uses. McDonald and associates[133] have postulated that an excess red cell mass may have an immediate sparing action on body proteins by displacing plasma volume and thereby reducing the amount of plasma protein needed to maintain circulation. Protein so spared, they stated, may be used for wound healing.

Somewhat less than the almost complete retention of red blood cells in the circulation of the recipient observed in Tables V and VI and in C. N. (Case 6), may possibly have occurred. In these studies, the total blood volume was determined by measuring the plasma volume and the hematocrit value of the peripheral blood. Snead and Ebert[191] and Hahn and associates [83, 84] have shown that red cell volumes as calculated from plasma volume and venous hematocrit give values about 25 per cent higher than when checked by viviperfusion, by radio iron distribution in tagged red blood cells, and by measurements before and after known massive bleeding.

Since the malnourished state has been shown quite uniformly to be associated with a contraction of blood volume,[2, 34, 123, 135, 155, 185, 211, 217] the use of whole blood transfusions during the preoperative preparation phase has the added beneficial effect of restoring this volume to normal levels before subjecting the patient to the trauma of operation. Lyons[123] felt that the unsteady state of patients with chronic infections and weight loss is primarily related to a reduced blood volume, a deficiency of total circulating hemoglobin, and to an excessive interstitial fluid volume. In this connection it would be of great importance to ascertain the effect on blood volume of oral dietary preparation alone, and of protein digest solutions given parenterally and orally. However, it would appear in the light of present knowledge that correction of this phase of the malnourished state can be most promptly and effectively brought about by whole blood transfusions.

That human plasma protein may not be a complete protein for the rat is suggested by the work of Hegsted and associates,[92] who found that when human plasma protein fed to rats was supplemented with isoleucine or with whole casein, better growth occurred than when equivalent amounts of protein were taken as human plasma protein alone. In contrast, Madden and Whipple,[128] Weech and Goettsch,[212] and Melnick and co-workers[138] found beef plasma protein to be the most effective of all proteins tested, in producing plasma protein regeneration in protein-depleted dogs. Similarly, hemoglobin on chemical analysis is low in isoleucine, cystine, and methionine.[18] Albanese,[6] employing the method of bio-assay in rats, which require isoleucine for growth and maintenance, found that hemoglobin failed to support weight in mature rats, unless supplemented by isoleucine. Robscheit-Robbins and associates[168] found that addition of methionine to hemoglobin solution increased its effectiveness in dogs. Miller[141] also found that dog hemoglobin given parenterally was well utilized to maintain weight and nitrogen balance in dogs. Its utilization, however, was improved by the addition of d. l. methionine, but was unaffected by the addition of isoleucine.

It would appear that in a person to be maintained by parenteral means there might be some benefit derived, from a nutritional viewpoint, of supplementing whole blood transfusions with a complete mixture of amino acids. This can be most practically done at present with a good digest of a complete protein. From studies here reported the greatest nitrogen retention occurred when whole blood plus 3000 c.c. of 5 per cent amigen in 5 per cent glucose solution was given intravenously.

At present, there are no actually objective means of deciding when a patient has had sufficient preoperative preparation. Such clinical criteria as return of appetite, loss of anorexia, and improvement of strength are helpful adjuncts and often appear when the drain of a state of negative nitrogen balance is replaced by a state of positive nitrogen balance. Certainly one should not expect marked weight gain, other than that associated with fluid replacement. The suggestion of Lyons[123] and Abbott and Mellors[2] of determining blood volume and returning a contracted blood volume to normal levels before embarking on a major operative venture is of real importance, but this does not reflect the

state of the protein stores. From the results in the patients reported, all of whom had lost from 20 to 33 per cent of their body weight, it would appear that about one week of intensive, parenteral, preoperative preparation may be sufficient. During this time, such patients should receive daily whole blood transfusions supplemented by an intravenous casein digest solution in amounts up to 18 Gm. of nitrogen. Under such a regimen, and without oral supplements, positive nitrogen balance can be achieved and poor-risk patients so prepared can be operated upon with risks comparable to similar uncomplicated cases.

SUMMARY AND CONCLUSIONS

1. The importance of a clear understanding by surgeons of protein metabolism and its related problems in the care of surgical patients is stressed.

2. A consideration of hemoglobin metabolism as it relates to general protein metabolism is presented.

3. In the preoperative preparation of patients for surgery, the necessity of replenishing depleted protein stores is stressed.

4. In the malnourished poor-risk patient, who cannot maintain nutrition by oral means, parenteral preoperative preparation is necessary and effective.

5. Positive nitrogen balance in man, using human plasma given intravenously as the sole source of nitrogen intake, can be attained.

6. Positive nitrogen balance in man, using whole human blood intravenously as the sole source of nitrogen intake, appears to be attained, although the protein contained in the red blood cells is not immediately and directly available for general body protein needs.

7. After daily whole blood transfusions in man, the major part of the injected red blood cells remain in the circulation of the recipient and account for the rise of total blood volume observed. Very little change in plasma volume is observed.

8. Positive nitrogen balance in man cannot be attained when giving intravenously amounts of an acid hydrolysate of casein fortified with tryptophane containing 6 Gm. of nitrogen.

9. Positive nitrogen balance in man cannot be attained when giving intravenously amounts of an enzymatic digest of casein containing 6 Gm. of nitrogen.

10. Positive nitrogen balance in man can uniformly be attained when giving intravenously amounts of an enzymatic digest of casein containing 18 Gm. of nitrogen.

11. A difference in mode of utilization of casein digests and of whole plasma protein given intravenously is noted. A possible explanation of this difference is presented.

12. From a nutritional viewpoint, supplementation of whole blood transfusions by amino acid solutions or casein digest may have a beneficial effect on nitrogen retention.

13. Malnourished, poor-risk patients can be adequately prepared for surgery by parenteral means alone, and when so prepared will stand operations of major magnitude with risks equal to those of similar uncomplicated cases.

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Book Reviews

Principles in Roentgen Study of the Chest. By William Snow. Springfield, Ill., 1946. Charles C Thomas, Publisher.

This monograph is an excellent one because of its simplicity and conciseness. The author, in the beginning, describes the various types of roentgenography followed by a discussion of normal lung findings. At the end of each chapter is an excellent group of representative roentgenograms demonstrating the points which the author wants to emphasize. After the consideration of the normal anatomy and roentgenologic findings, the various disease processes are taken up separately, the first part of each chapter being given over to the subject, with reference to illustrative roentgenograms at the end of each chapter. Special chapters deal with special chest problems in children and the roentgenologic demonstration of the thoracic circulatory system and the thoracic cage itself. The monograph is profusely illustrated as demonstrated by the 508 illustrations in the 397 page monograph. Illustrations are well produced.

The only criticism that the reviewer has of the book is that bronchiectasis, which is such a frequently encountered condition, is certainly inadequately considered.

Because of the conciseness of the work, it should be of great value to every physician.

Surgical Treatment of the Nervous System. By Bancroft, F. W., and Pilcher, C., editors. Pp. 534, with 298 illustrations. Philadelphia, 1947, J. B. Lippincott Company.

This is a compilation of twenty chapters, seventeen of them written by an individual and three of them written by a senior and junior author. The associate editor wrote five chapters.

Since there are many contributors, there is considerable chapter variation in manner of presentation and quality. There are some very well written chapters, but so many are mediocre that the book as a whole is a disappointment. Perhaps the deficiencies of the book are due in part to the trying time in which it was compiled but it seems that all chapters should have a common objective, which is apparently not the case. As written, the general surgeon and general practitioner will find it a valuable reference book but with the exception of a few chapters the neurosurgeon will profit little by reading it. A similar but more comprehensive treatise written as a ready reference for the nuerosurgeon would be most valuable. Some chapters have no bibliography, others have a list of references at the end of the chapter, and a few have documented the text by specific reference to the bibliography.

Chapter 1, The General Principles of Neurosurgical Technique, is a description of standard neurosurgical technique, anesthesia in neurosurgery, technique of pneumoencephalography, angiography, etc.

Chapter 2, The Surgery of Infantile Hydrocephalus, is a discussion of the author's views concerning the diagnosis, selection of cases for operation, treatment, and prognosis. Toxoplasmosis, one of the more common causes of infantile hydrocephalus, is not even mentioned.

Chapter 3, Craniocerebral Trauma. In this chapter in addition to the usual textbook discussion of subdural hematoma, there is added a one-page discussion of subdural hematomas in children, including some information recently published in the periodic literature.

Chapter 4, Cranioplasty, is a fairly good review of modern methods of skull defect repair but would be much more easily understood if better illustrated. There is a page of colored photography which catches the eye but is very disappointing when one attempts to find the details referred to in the legend.

Chapter 5, Brain Abscess, is one of the better chapters. It is short yet contains many of the problems encountered in treating these difficult lesions. The author admits that difficult situations may be encountered and that the surgeon may make serious errors. Vincent's method of excision of abscesses is briefly discussed. Even since this book was written a more radical modification of Vincent's methods seems to be gaining favor.

Chapter 6, Osteomyelitis of the Skull, is a good discussion of sinus and mastoid infections in their relation to osteomyelitis of the skull. It seems unfortunate that a neurosurgeon sufficiently familiar with osteomyelitis of the skull could not be found to write this chapter. It is obvious that the author has had a large experience with osteomyelitis of the skull and in general the opinions expressed and the technique described conform to good neurosurgical practice, yet there are minor variations from accepted neurosurgical practice, such as chiseling on the skull which contains a traumatized brain. The important subject of bone regeneration after osteomyelitis is dismissed with a statement that in some instances bone regeneration serves to reduce or even correct the deformity.

Chapter 7, Tumors of the Skull, is a good but short chapter (seven pages). Eosinophilic granuloma, a recently described lesion of bone, is included. The use of fibrin film to repair dural defects is recommended by the author as though it were an accepted procedure.

Chapter 8, Tumors of the Meninges. After some very brief general remarks on meningiomas, the operative technique for meningiomas is discussed. In general, there is little to praise or severely criticize in this chapter, but one might disagree with some of the author's technique, that is "Deeper dissection may be done more gently and with less trauma to the adjacent brain by a dissecting finger." Obviously, the author of Chapter 10 is not of this opinion, for he writes "once the surface of the tumor is exposed, gentle dissection is less destructive and less hemorrhagic than crude finger enucleation."

Chapter 9, Tumors of Cranial Nerves, contains many informative illustrations but like the preceding chapter gives the impression of being compiled without great effort on the part of the authors. Only one reference is given.

The upright or sitting position for operation is considered to be by far the most favorable for operation in the posterior cranial fossa; its advantages and disadvantages are discussed but the reader is not cautioned that air embolus can occur.

Total and partial removal of eighth nerve tumors is discussed but the authors do not indicate whether their own practice is to remove these tumors totally or partially. Choice of operation is dismissed with the noncommittal statement that "surgeons differ in their views regarding the most desirable method, but sound surgical judgment demands that the method be chosen that best meets the circumstances encountered in each individual patient."

Chapter 10, Intrinsic Tumors of the Cerebrum. The surgical pathology of most of the intrinsic tumors of the brain is briefly discussed followed by a section entitled clinical discussion, in which the results of surgery are given and a very brief discussion of the symptomatology and findings in the various types of tumor is included. Under operative methods it is obvious that only the author's individual technique is considered. A short paragraph on prevention of cortical ruptures is interesting and has merit but one wonders if the methods described are always effective in its prevention. The author is very pessimistic about the results of x-ray therapy in intrinsic tumors of the cerebrum.

Chapter 11, Tumors of the Hypophysial Region. Much of this chapter is anatomy, surgical pathology, and diagnosis of suprasellar lesions. Fig. 66 which the same author uses in Chapter 9 would have been more appropriate here. Treatment is discussed in more or less standardized fashion giving the impression that chromophylic adenoma, craniopharyngioma, and suprasellar cholesteotoma are frequently totally removed without insurmountable difficulty. Hyperthermia resulting from trauma to the hypothalamus is not mentioned.

Chapter 12, Intrinsic Tumors of the Cerebellum and Brain Stem, is an excellent chapter with absence of mediocrity found in many of the other chapters. It is documented. The author gives not only his own opinion or procedure but also that of others and discusses factors favorable and unfavorable.

Chapter 13, Vascular Anomalies of the Brain, is very much the same material contained in a paper published in 1946 by the author of this chapter. It advocates excision of these lesions if possible and three cases in which excision was performed are reported.

Chapter 14, Surgery of Disorders of the cranial Nerves, is one of the better chapters in the book. It is quite inclusive, giving not only the author's procedures but also all others, including even the most recent literature. There are a number of very informative line drawings, and a good bibliography is appended.

Chapter 15, Diseases Characterized by Involuntary Movements, is a good and well-documented discussion of these movements and their treatment. Complete detailed description of the operation is given. Much is said in evaluation of the operative treatment for these conditions and it seems to be well balanced without undue conservatism or enthusiasm for the operation.

Chapter 16, Epilepsy Due to Atrophic Cerebral Lesions, is a short but well-written chapter, most of it a description of indications for operation and technique of operation.

Chapter 17, Surgery of the Spinal Cord, is a narration for the most part of the author's opinion and practice, with no bibliography. It is well illustrated but otherwise gives the impression of having been composed without great effort.

Chapter 18, Surgical Lesions of Peripheral Nerves, is a good standard discussion with brief mention of most of the recent developments. Such problems as nerve grafts, causalgia, and phantom limb pain with cortical excision for its relief are considered and one of the admirable features is the fact that the author freely gives his opinion in many controversial matters.

Chapter 19, Surgery of the Sympathetic Nervous System, is a well-written and illustrated forty-four pages. This is one of the better chapters in the book. Much of it is description of various types of sympathectomy followed by a discussion of their application.

Chapter 20, Chemotherapy in Neurosurgery, is a very short discussion of some of the general principles of the use of sulfonamides and penicillin in neurosurgery.

It is to be hoped that this is only the first of many future editions of a comprehensive up-to-date text and reference book of neurosurgery.

Gynecological and Obstetrical Pathology. By Emil Novak, A.B., M.D., D.Sc., F.A.C.S., ed. 2, Philadelphia, 1947, W. B. Saunders Company.

This book is so well known by gynecologists, obstetricians, and pathologists that mention of its value is unnecessary. Although neither an exhaustive treatise nor a reference, the book covers the material adequately in a clear concise style. Suitable bibliographic references for additional study are supplied at the end of each chapter.

The second edition has brought the material up to date and has many new illustrations. Most of the illustrations are excellent. However, those showing the various gross vulvar lesions are unsatisfactory.

The book should appeal to pathologists as well as gynecologists and residents in training.

Radiology for Medical Students. By Hodges, F. J., Lampe, I., and Holt, J. F. Pp. 424. Chicago, 1947, The Year Book Publishers, Inc. $6.75.

This little book is the first adequate single volume presentation of the principles of present-day roentgenologic diagnosis and radiation therapy. While it is designed for the use of medical students and has been organized around the course presented at the University of Michigan it would constitute a very adequate and complete introduction to radiology for any physician who wishes to know more about the fundamentals of the radiologic approach to medical problems both diagnostic and therapeutic.

Thorough-going courses in radiology are relatively new in the medical curriculum and the authors of this book have been aware of the usual problem that arises as to whether to

present merely a few fundamental considerations or to attempt to present a wealth of detail. It seems to this reviewer that the authors have made a very wise choice in steering, as far as text is concerned, a more or less middle ground. The emphasis has certainly been, particularly in the diagnostic section, on principles without too much attempt to present all of the various diagnostic possibilities and rare and unusual conditions which might be illustrated.

Very excellent and concise introductory material is presented on the history of the development of radiology and there are also excellent brief sections on the physics of diagnostic roentgenology, the physics of therapeutic radiology and, of special interest, material on the biologic and therapeutic effects of radiation. This latter material is particularly difficult of access in concise and understandable form and seems particularly valuable for inclusion in an elementary treatise of this sort.

Of special merit in the diagnostic section is the emphasis on the method of approach both in planning and in carrying out the x-ray study and in interpretation of the findings. It is this emphasis on the presentation of what might be called the underlying philosophy of radiology that principally distinguishes this book in the reviewer's mind.

The section on the tissue effects of radiation is of the greatest importance and there is an excellent presentation of the fundamental differences between radiosensitivity and radiocurability of tumors. Also very important is the emphasis on the late effects of the intensive irradiation for destruction of neoplasms of which both the physician and the patient should be aware at the time the irradiation is carried out.

No attempt has been made to be dogmatic as to the choice of therapeutic methods recommended and it is well emphasized that the radiation method is not in competition with surgery but rather that the two methods have specific indications and often are supplementary.

This volume is not intended to be in any way a handbook or atlas of radiology for the diagnosis and treatment of disease but it is a very well thought out and readable presentation of the fundamentals of the subject.

The 1946 Year Book of Neurology, Psychiatry and Neurosurgery. Edited by Neurology: Hans H. Reese, M.D., Professor of Neurology and Psychiatry, University of Wisconsin Medical School and Mabel G. Masten, M.D., Associate Professor Neuropsychiatry, University of Wisconsin Medical School; Psychiatry: Nolan D. C. Lewis, M.D., Director, New York State University; Neurosurgery: Percival Bailey, M.D., Professor Neurology and Neurological Surgery, University of Illinois. Pp. 732, with 103 illustrations. Chicago, 1946, The Year Book Publishers, Inc. $3.75.

This book is comprised of abstracts of articles which the editors consider representative of the year's literature in these fields. The editors possess wide experience and are capable of proper selection of articles and of making proper criticism of them. It is unfortunate that they do not comment more frequently and in greater detail concerning their opinions of the articles reviewed. Such an addition would give the book better continuity and the abstracts proper relative significance. The subject matter of the various fields is well covered. Both the foreign and American literature is abstracted.

The section on neurology includes articles on neuroanatomy, neurophysiology, neuropathology, convulsive disorders, diseases of the central nervous system, and neurologic diagnostic procedures. The abstracts are complete, in fact, some are too long and could be adequately reviewed with greater brevity.

The section on psychiatry includes articles on specific childhood psychiatric problems, the psychoses, the psychoneuroses, and special therapy in psychiatry. There are also many abstracts dealing with military psychiatric problems. The abstracts in this section are concise; the field of psychiatry is well reviewed.

The section on neurosurgery includes information on peripheral and sympathetic nerve surgery, purulent infections of the central nervous system, herniated discs, spinal cord and craniocerebral injuries, vascular lesions, and intracranial tumors. This is the first year that

there has been a separate section of the Year Book devoted to the field of neurosurgery. The advisability of having such a section is readily apparent to the reader. It is an excellent addition and should be continued.

This year's Year Book is especially valuable since there is more comprehensive coverage of more closely allied fields of interest than in previous years. It is emphasized that all persons even with an indirect interest in neurology, psychiatry, and neurosurgery should read this book.

Diseases of the Adrenals. By Louis J. Soffer, M.D., Philadelphia, 1946, Lea & Febiger.

This book is written well and is easy and interesting to read. It contains a thorough summary of the recent advances in the study of the physiology of the adrenal cortex including the chemistry of the steroid hormones of the cortex and the function of these compounds. The physiologic concepts of adrenal cortical function are very nicely correlated with clinical conditions. The chapters dealing with Addison's disease are especially informative. The details of treatment are good, but the discussion of the treatment of crisis in Addison's disease is a bit too brief for the person who has had little experience with the disease. The discussion of the adrenogenital syndrome is rather complicated as it necessarily must be. The evaluations of diagnostic aids such as 17—ketosteroid analysis and perirenal air insufflation are conservative and fair. The indications for operation and the precautions regarding therapy immediately after removal of an adrenal cortical tumor are thoroughly discussed. In the discussion of the diagnosis of pheochromocytoma no mention is made of the histamine provocative test described by Roth. This test is simple and should be of much use in detecting this condition. The extensive bibliography covering the subject of adrenal physiology and pathology is worth a great deal. There are several errors in text references to the bibliography. This book should be very useful for physicians in general internal medicine as well as for physicians limiting their practice to metabolic diseases.

Medicine in the Changing Order. Report of the New York Academy of Medicine and the Changing Order. Pp. 240. New York, 1947, Commonwealth Fund. $2.

In 1942 the New York Academy of Medicine appointed a committee to study the problems of medical care, a committee which during the course of its deliberations was wisely designated as a Committee on Medicine and the Changing Order. This committee, made up largely of physicians, but with representation from allied professions and social groups, has had the advice and counsel of a large number of distinguished community leaders representing diversified interests and points of view. Subcommittees dealt with medical education, graduate and postgraduate medical education, internships, hospitals, administration of public health services, extension of medical services, cost of diagnostic and consultant services, industrial medicine, rural medicine, nursing, and dentistry.

The committee has already sponsored a series of distinguished monographs which represented, however, the points of view of the respective authors, not of the committee. Several of these monographs have already been reviewed in these columns. The current volume signed by the committee constitutes the report and conclusions of its deliberations. At the same time it serves as an admirable summary of the entire series.

Approaching its task from the historical perspective, the committee has analyzed the current problems and needs of medical care and in a thoroughly objective manner has attempted to appraise the various suggestions advanced for better medical service. Throughout the report, emphasis is placed upon quality as well as quantity of care, and upon the necessity of greater attention to the preventive aspects of medical service.

The report is packed with recommendations which are made boldly and without evasive qualifications. The committee supports the growing tendency toward group practice, urges more extensive voluntary health insurance aided by governmental subsidy if necessary, but

rejects compulsory insurance. It advocates expansion of health services and the construction of new hospitals and health centers radiating into rural areas from metropolitan centers. Among the many other recommendations are proposals for medical and nursing education and licensing, and for hospital construction and administration.

Throughout the book runs a dominant theme of the need for greater recognition of the social obligations of medicine and attention to social and economic forces without sacrifice of the scientific aspects which have developed more rapidly in recent years. Few readers will agree with all the proposals and recommendations but all will recognize this volume as a thought-provoking and forthright analysis of medicine's obligation to adapt itself to changing social conditions.

Postgraduate Obstetrics. By William F. Mengert, M.D., Pp. 363, with 123 illustrations. New York, 1947, Paul B. Hoeber, Inc.

This book is a brief review of practical clinical obstetrics. Virtually all theoretical discussions have been eliminated. On the whole, the material is well presented and the illustrations, although limited, are good. The book considers only common complications of pregnancy.

It is a little difficult to understand how the book can be extensively used as it is too brief for medical students and too incomplete for the practitioner dealing with specific obstetric problems in practice.

The widest application of this material would probably be for the physician desiring a brief review of obstetrics before beginning practice.

Penicillin in Neurology. By A. Earl Walker, M.D., Associate Professor of Neurological Surgery, the University of Chicago, and Herbert C. Johnson, M.D., Resident Neurological Surgeon, The University of Chicago. Pp. 204 with 95 illustrations. Springfield, Ill., 1946, Charles C Thomas, Publisher. Cloth. $5.

The jacket on this volume states "this monograph presents (1) the results of studies of the dispersion and absorption of penicillin when administered by intrathecal injection and (2) the effect of the drug on nervous tissue in health and disease. On the basis of these investigations and clinical experiences, the rational use of penicillin in neurological disorders is discussed, giving the book a wide range of appeal among physicians, surgeons and research workers."

The introductory chapters are devoted to a consideration of penicillin in general and to the routes of administration of the drug with particular reference to the distribution of penicillin in the central nervous system. Then follow experimental and clinical observations detailing the toxic effects of penicillin upon the central nervous system. These and subsequent investigations indicate that toxic reactions are related to the quantity of the antibiotic introduced intrathecally and into the ventricular spaces. Therapy of suppurative meningitis is then presented with the important recommendation that penicillin must be injected intrathecally as well as administered parenterally for the most satisfactory results. There is a sound discussion of the therapy of pyogenic infections of the skull and brain, as well as the diseases of the spinal cord. A glaring weakness of this monograph is the brief and incomplete discussion of penicillin in the treatment of syphilis of the nervous system. This chapter might well have been omitted without detracting from the purpose and value of the monograph. The work concludes with a brief discussion of other antibiotics such as streptomycin, streptothricin, actinomycin, and clavacin. The volume is well indexed, profusely illustrated, and the publisher has utilized skill and good taste in producing an attractive book.

On page 150 the authors touch upon an important theme which has distressed many clinicians treating suppurative disease of the central nervous system with penicillin. They refer to discretion on the part of the physician in treating infected cases of spina bifida where

there is serious derangement of the nervous system. Eradication of the infection in some cases will lead to major social and economic complications. In older children and adults suppuration of the central nerves causes irreparable damage to the central nervous system, and the use of a potent antibacterial agent like penicillin has eliminated the infection but has left patients hopelessly incompetent. However, brilliant therapeutic results frequently ensue in some of the most desperately ill patients, and the physician has no choice but to treat all of the patients with this expectation in view.

The monograph should be of interest to students in this field, and individuals in the related specialties, but the general physician can find more suitable information elsewhere.

Parenteral Alimentation in Surgery, With Special Reference to Proteins and Amino Acids. By Robert Elman, M.D., Associate Professor of Clinical Surgery, Washington University School of Medicine. Pp. 284, with 31 illustrations. New York, 1947, Paul B. Hoeber, Inc.

This monograph dealing with work for which the author was awarded the quinquennial Samuel D. Gross prize of the Philadelphia Academy of Surgery is commended to both the physician and the surgeon. The introductory chapter on the history of parenteral alimentation is interesting and informative. The early chapters of the book deal with the intriguing thesis of supplying all necessary nutritional elements by parenteral means. Chapters V through X relate to the problem of parenteral protein therapy. The material is well presented and complete, although there is a tendency to gloss over controversial material. Not enough stress seems to have been paid to blood volume changes in relation to malnourished states and in relation to the studies relating to the use of amino acid solutions.

Even though parenteral alimentation appears to be effective, and positive nitrogen balance can be achieved, the author wisely states that it should be considered as a temporary expedient for oral alimentation. It should be used as a means of clearing temporary hurdles with the ultimate aim in treatment to restore the patient as rapidly as possible to such a state that he may take all his nutritional requirements by mouth.

In spite of differences of opinion among workers in the field of protein therapy, particularly as it relates to surgical patients, this book is a very valuable contribution and marks a real advance of the science of nutrition as it can be applied clinically.

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Published by THE C. V. MOSBY COMPANY, 3207 Washington Blvd., St. Louis 3, U.S.A.

Great Britain Agents: Henry Kimpton, Ltd., 26 Bloomsbury Way, London, W.C.1.
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